BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of The original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
Please do not report the images to the
Image Problem Mailbox.**

JAN DELAVAL

PLEASE

Access DB# 77818

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Josephine Young Examiner #: 79813 Date: 10-11-2002

Art Unit: 1623 Phone Number 308-1201 Serial Number: 09/832,818

Mail Box and Bldg/Room Location: ~~CM1 8E17~~ (MB 8B19) Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Activation of natural killer cells by adenosine A3 receptor agonists

Inventors (please provide full names): FISHMAN, Pnina

Earliest Priority Filing Date: 04-12-2001

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Important concepts:
cmpds and their uses
diseases associated w/
NK cells
a) cmpds for use in
diseases related to
NK cells

see claims (4-6)

Important claims:
3-6
29-32

Please search:
(1) cmpd
(2) method to activate NK cells using cmpd
(3) text/concepts of claim 1 (see attached)

STAFF USE ONLY

Searcher: Jan

Searcher Phone #: 4458

Searcher Location:

Date Searcher Picked Up: 10/20/02

Date Completed: 10/21/02

Searcher Prep & Review Time:

Clerical Prep Time: 90

Online Time: + 180

Type of Search

NA Sequence (#)

AA Sequence (#)

Structure (#) V

Bibliographic

Litigation

Fulltext

Patent Family

Other

Vendors and cost where applicable

STN ✓

Dialog

Questel/Orbit

Dr.Link

Lexis/Nexis

Sequence Systems

WWW/Internet

Other (specify)

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

PTO-1590 (8-01)

National Library of Medicine - Medical Subject Headings

2002 MeSH

MeSH Descriptor Data

Return to Entry Page

MeSH Heading	Killer Cells, Natural
Tree Number	A11.118.637.555.567.537
Tree Number	A15.145.229.637.555.567.537
Tree Number	A15.382.490.555.567.537
Tree Number	A15.382.520.520.425
Annotation	cells spontaneously cytotoxic to tumor cells; A 11 qualif; subpopulations: coord IM with LYMPHOCYTE SUBSETS (IM)
Scope Note	Cells responsible for spontaneous cytotoxicity of a variety of tumor cells without prior immunization. These natural killer cells are found in non-immune humans and experimental animals and are thought by some to be the same as KILLER CELLS (killing by antibody-dependent cell cytotoxicity), but they can also kill in the absence of antibody.
Entry Term	NK Cells
Entry Term	Natural Killer Cells
Allowable Qualifiers	CH CL CY DE EN IM ME MI PA PH PS RA RE RI SE TR UL US VI
Previous Indexing	Cytotoxicity, Immunologic (1978-1982)
Previous Indexing	Immunity, Cellular (1976-1982)
Previous Indexing	Killer Cells (1978-1982)
History Note	83
Unique ID	D007694

MeSH Tree Structures

Cells [A11]

1: Exp Cell Res. 2001 Oct 1;269(2):230-6. Related Articles,

ELSEVIER FULL-TEXT ARTICLE

The A3 adenosine receptor as a new target for cancer therapy a chemoprotection.

Fishman P, Bar-Yehuda S, Barer F, Madi L, Multani AS, Pathak S.

Laboratory of Clinical and Tumor Immunology, Rabin Medical Center, Peta Tikva, 49100, Israel. pfishman@post.tau.ac.il

Adenosine, a purine nucleoside, acts as a regulatory molecule, by binding to specific G-protein-coupled A(1), A(2A), A(2B), and A(3) cell surface recept We have recently demonstrated that adenosine induces a differential effect o tumor and normal cells. While inhibiting in vitro tumor cell growth, it stimul bone marrow cell proliferation. This dual activity was mediated through the adenosine receptor. This study showed that a synthetic agonist to the A3 adenosine receptor, 2-chloro-N(6)-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA), at nanomolar concentrations, inhibited tumor cell growth through a cytostatic pathway, i.e., induced an increase number of cell the G0/G1 phase of the cell cycle and decreased the telomeric signal. Interestingly, Cl-IB-MECA stimulates murine bone marrow cell proliferatio through the induction of granulocyte-colony-stimulating factor. Oral administration of Cl-IB-MECA to melanoma-bearing mice suppressed the development of melanoma lung metastases (60.8 +/- 6.5% inhibition). In combination with cyclophosphamide, a synergistic anti-tumor effect was achieved (78.5 +/- 9.1% inhibition). Furthermore, Cl-IB-MECA prevented th cyclophosphamide-induced myelotoxic effects by increasing the number of white blood cells and the percentage of neutrophils, demonstrating its efficac a chemoprotective agent. We conclude that A3 adenosine receptor agonist, C IB-MECA, exhibits systemic anticancer and chemoprotective effects. Copyri 2001 Academic Press.

PMID: 11570815 [PubMed - indexed for MEDLINE]

h cb h g e e e fcg h g g c e e e b b e

Experimental Cell Research
Volume 269, Issue 2 , 1 October 2001, Pages 230-236

doi:10.1006/excr.2001.5327 Cite or link using doi

Regular Article

The A3 Adenosine Receptor as a New Target for Cancer Therapy and Chemoprotection

Pnina Fishman[b, a, 1], Sara Bar-Yehuda[b, a], Faina Barer[b, a], Lea Madi[b, a], Asha S. Multani[c] and Sen Pathak[c]

[a] Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Tel-Aviv University Sackler Faculty of Medicine, Rabin Medical Center, Petach-Tikva, 49100, Israel
[b] Can-Fite Biopharma Ltd, Kiryat-Matalon, Petach-Tikva, Israel
[c] Department of Cancer Biology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, 77030

Received 14 February 2001; revised 10 July 2001. Available online 1 March 2002.

Abstract

Adenosine, a purine nucleoside, acts as a regulatory molecule, by binding to specific G-protein-coupled A_1, A_{2A}, A_{2B}, and A_3 cell surface receptors. We have recently demonstrated that adenosine induces a differential effect on tumor and normal cells. While inhibiting *in vitro* tumor cell growth, it stimulates bone marrow cell proliferation. This dual activity was mediated through the A3 adenosine receptor. This study showed that a synthetic agonist to the A3 adenosine receptor, 2-chloro-N^6-(3-iodobenzyl)-adenosine-5'-*N*-methyl-uronamide (Cl-IB-MECA), at nanomolar concentrations, inhibited tumor cell growth through a cytostatic pathway, i.e., induced an increase number of cells in the G0/G1 phase of the cell cycle and decreased the telomeric signal. Interestingly, Cl-IB-MECA stimulates murine bone marrow cell proliferation through the induction of granulocyte-colony-stimulating factor. Oral administration of Cl-IB-MECA to melanoma-bearing mice suppressed the development of melanoma lung metastases (60.8 ± 6.5% inhibition). In combination with cyclophosphamide, a synergistic anti-tumor effect was achieved (78.5 ± 9.1% inhibition). Furthermore, Cl-IB-MECA prevented the cyclophosphamide-induced myelotoxic effects by increasing the number of white blood cells and the percentage of neutrophils, demonstrating

h ce ce ec c ce ce b ce c

its efficacy as a chemoprotective agent. We conclude that A3 adenosine receptor agonist, Cl-IB-MECA, exhibits systemic anticancer and chemoprotective effects.

Author Keywords: A3 adenosine receptor; melanoma; bone marrow; synthetic A3 agonists; neutrophils; G-CSF

---

[1] To whom reprint requests should be addressed. Fax: 972-9-9233228. E-mail: pfishman@post.tau.ac.il.

Experimental Cell Research
Volume 269, Issue 2 , 1 October 2001, Pages 230-236

This Document
- **Abstract**
- Abstract + References
- PDF (170 K)

Actions
- E-mail Article

Home | Journals | Abstract Databases | Reference Works | My Profile | Alerts | Help

h c e ce ec c c e ce b c e c

SCIENCE & TECHNOLOGY
February 12, 2001
Volume 79, Number 7
CENEAR 79 7 pp.37-40
ISSN 0009-2347

[Previous Story] [Next Story]

A_3 RECEPTORS

Compounds that activate or inhibit adenosine A_3 receptors are being studied for potential therapeutic use in heart disease and cancer

STU BORMAN,C&EN WASHINGTON

For about the past decade, researchers in government, academic, and industrial labs have been pursuing compounds that activate or inhibit adenosine A_3 receptors. These cell-membrane proteins have a wide range of physiological and disease-related effects and are thus considered promising drug targets.

Those efforts are now beginning to come to fruition, as a number of A_3 activators and inhibitors (agonists and antagonists, respectively) enter clinical trials for several human diseases. And such A_3 ligands are also of interest as tools that can help scientists learn more about the

COURTESY OF KEN JACOBSON, DOV BARAK, AND STEFANO MORO

BOUND TO FIT View of th A_3 r c ptor

Related
'Synthetic Makes Its [C&EN, 2000]
Neurosci Ultimate Walk [C&EN, 1999]

Related
Kenneth Jacobson
Pier Giov Baraldi
Christa E
Gary L. S
Beverly I
Pnina Fis
Bruce T.
Mortimer

E-mail th a friend
Print this
E-mail th

h b c g ce c e ece h

role of A_3 receptors in the body--functions that have not yet been fully characterized.

from ab ve shows th arrangement of its s v n transmembrane α-helices and a bound agonist, IB-MECA [*N*^{6}-(3-i dobenzyl)-ad nosine-5′-*N*-methyluronamide]. The receptor's van der Waals surface and loops connecting the seven transmembrane helices are omitted.

A_3 proteins are G-protein-coupled receptors that are normally activated by adenosine. In addition to being the main component of adenosine triphosphate, the energy currency of cells, adenosine is a neuromodulator in that it affects nervous system function but does not act as a neurotransmitter per se. A_3 receptors also can be activated by inosine, a major metabolite of adenosine.

The receptors, which are expressed in a variety of body tissues, have functional effects that are surprisingly contradictory. When activated only moderately, they have a cytoprotective role--such as reducing damage to heart cells from lack of oxygen or protecting cells from apoptosis (programmed cell death). But at high levels of stimulation they can actually cause cell death. A_3 receptor agonists and antagonists are thus being tested for treatment of a number of conditions, ranging from heart disease to cancer.

THE A_3 RECEPTOR is actually part of a family of four related adenosine receptor types, and its three siblings also play important functional roles. The A_1 and A_{2a} receptor subtypes protect organs such as the heart and brain under conditions of stress. And the A_{2b} subtype, which is expressed on mast cells in inflamed tissues and tends to increase intracellular calcium levels, is considered a promising target for asthma drugs.

Ligands for the A_3 receptor were designed and synthesized by government and academic groups before the receptor's biological functions were at all well defined, and the availability of these ligands has greatly facilitated studies on the receptor's biochemistry and function. The ligand development research thus exemplifies how fundamental biochemical studies can help lead to future biomedical advances.

One of the most active research groups among those that have developed A_3-targeted ligands is that of Kenneth A. Jacobson, chief of the Molecular Recognition Section of the Laboratory of Bioorganic Chemistry at the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK), Bethesda, Md. Jacobson and coworkers have developed both agonists and antagonists that

are potent and selective for these receptors.

But a team led by Pier Giovanni Baraldi, director of the department of pharmaceutical science at Ferrara University, in Italy, made the most recent advance in the A_3 field last December when it reported the most potent and selective human A_3 adenosine antagonist found to date [*J. Med. Chem.*, **43**, 4768 (2000)]. Professor of medicinal chemistry Ad P. IJzerman and coworkers at Leiden University, in the Netherlands, have also synthesized a number of A_3-selective agonists and antagonists.

The A_3 receptor was first cloned from a rat brain cDNA library in 1992 by Gary L. Stiles, chief of the Division of Cardiology at Duke University Medical Center, and the first human A_3 receptor was cloned the next year by Marlene A. Jacobson of the department of pharmacology at Merck Research Laboratories, West Point, Pa., and coworkers. Merck has a patent on the human A_3 receptor.

IN THE EARLY '90S, Ken Jacobson (no relation to Marlene) also started working on A_3, at a time when nobody had any idea what physiological functions the A_3 receptor had in the body. Jacobson explains that he and his coworkers "began by making selective ligands, hoping pharmacologists would use them to establish a role for the receptor." His team found selective A_3 agonists in 1994, and "these are still the principal selective agonists used in many labs that study adenosine receptors."

The usual antagonists for adenosine receptors in general "are the xanthine drugs, of which caffeine and theophylline are probably the best known," Ken Jacobson says. "These block most subtypes of adenosine receptors but don't block A_3 receptors very well."

The first nonxanthine A_3 antagonists were discovered by the Merck group. The NIDDK team subsequently found other nonxanthine antagonists by "going to molecular diversity to get leads," Ken Jacobson says. "We identified a bunch of heterocycles, including flavonoids, pyrazoloquinazolines, 1,4-dihydropyridines, 1,3-diacylpyridines, and 1-alkylpyridinium salts. We optimized some of those and eventually ended up with selective A_3 antagonists of close to nanomolar potency."

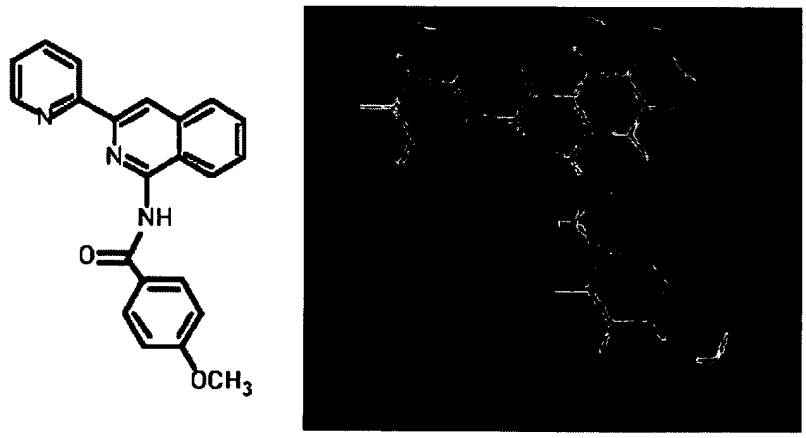
Ken Jacobson and coworkers recently characterized the preferred conformation of pyridine derivatives in the binding site of A_3 receptors. They synthesized ring-constrained analogs, superimposed structurally diverse A_3 antagonists to arrive at a unified model,

synthesized combinatorial libraries of potential A_3 ligands, and carried out site-directed mutagenesis on the related A_{2a} receptor to determine the mechanism of A_3 binding.

Like the NIDDK group, Baraldi and coworkers have synthesized a number of A_3 antagonists, including the most potent and selective ones identified so far, although some found by Ken Jacobson's team are not far behind. The Italian group also prepared the first radiolabeled A_3 adenosine antagonist as a tool for further characterizing the A_3 receptor subtype and clarifying its functional role in the body.

IJzerman and coworkers have synthesized a variety of A_3-active antagonists as well as some "partial" agonists--ligands that activate human A_3 receptors in a limited way. This actually might be a desirable property, IJzerman says, because of the A_3 receptor's tendency to cause severe side effects when overstimulated. He believes chronic low-level stimulation of the receptor could be just the ticket to bring out the receptor's desirable cerebroprotective and cardioprotective properties.

Other groups working on A_3 inhibition and activation include professor Christa E. Müller and coworkers at the Pharmaceutical Institute at the University of Bonn, in Germany, who recently developed a tritiated imidazopurinone derivative as a new A_3 antagonist radioligand. The group is currently preparing a manuscript on the work.



ANTI-INFLAMMATORY A_3 antagonist VUF 8504, a potential anti-inflammatory agent synthesized by IJzerman and coworkers, is shown as a line drawing and as a van der Waals surface. In the latter representation, regions of positive charge are shown in blue and regions of negative

h b c g ce c e ece h

charge are shown in red.

A_3 KNOCKOUT ORGANISMS--mice with deficient expression of the A_3 receptor gene--were reported last year by Marlene Jacobson and coworkers at Merck. They currently are being used worldwide in a range of studies on physiological functions of the A_3 receptor and effects of A_3 inhibition on a variety of disease models. For example, the Merck group, in collaboration with research assistant professor of medicine Beverly H. Koller and coworkers at the University of North Carolina, Chapel Hill, has used A_3 knockouts to determine physiological effects of adenosine and inosine on A_3-related changes in blood vessel permeability.

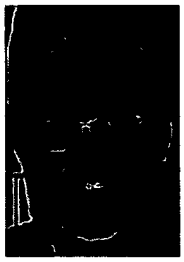
With potent ligands that activate or inhibit A_3 receptors in hand, it wasn't much of a conceptual leap to speculate that some of these compounds might be good leads for drug discovery, and that has turned out to be true. For example, Pnina Fishman, head of the Laboratory of Clinical & Tumor Immunology at Felsenstein Medical Research Center, Petach Tikva, Israel, and coworkers have published a number of papers on the use of A_3 agonists for shrinking tumors. "The differential effect of A_3 agonists on normal and tumor cells is, in my opinion, the most fascinating phenomenon regarding the activation of this receptor," Fishman notes. "We have established a biotech company, Can-Fite Biopharma (also in Petach Tikva), that focuses on the development of A_3 agonists as anticancer and chemoprotective agents."

In addition, Baraldi has been collaborating with Medco Research, Research Triangle Park, N.C., a subsidiary of King Pharmaceuticals, Bristol, Tenn., to develop A_3-active therapeutic agents. IJzerman believes some of his ligands might make good drug candidates as well.

"The hottest area defined so far is cardioprotection for A_3 receptor agonists," Ken Jacobson says. "They really work dramatically well." The concept has been validated now by genetic overexpression of the A_3 receptor in mice and subsequent limitation of damage in models of cardiac ischemia--a decrease in blood supply to the heart owing to obstruction or constriction.

Associate professor of medicine and pharmacology Bruce T. Liang and coworkers at the University of Pennsylvania, working in collaboration with the NIDDK group, were first to show that genetically engineered cardiac myocytes overexpressing human A_3 rece ptors are highly resistant to the deleterious effects of ischemia.

The Penn-NIDDK team also has found a synergistic cardioprotective interaction between A_1 and A_3 receptors. "The concept is that agonists coactivating both A_1 and A_3 receptors are likely to provide protection from ischemia at lower doses than those required for selective A_1 or A_3 agonists and could thus have fewer side effects," Liang explains.



KEN JACOBSON

A_3 agonists that limit heart attack damage to cardiac muscle cells are currently being studied as possible drug prospects by the Penn-NIDDK group. Such A_3-targeted drugs could be administered either prospectively prior to an operation with a high risk of cardiac ischemia or retrospectively to treat ischemia after a heart attack has already occurred. Studies on the cardiovascular role of the A_3 receptor are being carried out at Merck as well.

A_3 AGONISTS may also have applications in stroke treatment. "We have found that chronic administration of an A_3 agonist is highly cerebroprotective in a model of global cerebral ischemia in gerbils," Ken Jacobson says. "The benefit is seen in preservation of neurons of the hippocampus and in the survival and behavior of the animals following recovery."

There currently is no drug on the market "to limit the spread of excitotoxic damage in the brain during the first few days following a stroke," he adds. "We have evidence that modulating A_3 receptors may be useful in this regard. A_3 agonists would have fewer side effects than A_1 agonists, which may also be cerebroprotective but tend to depress heart function."

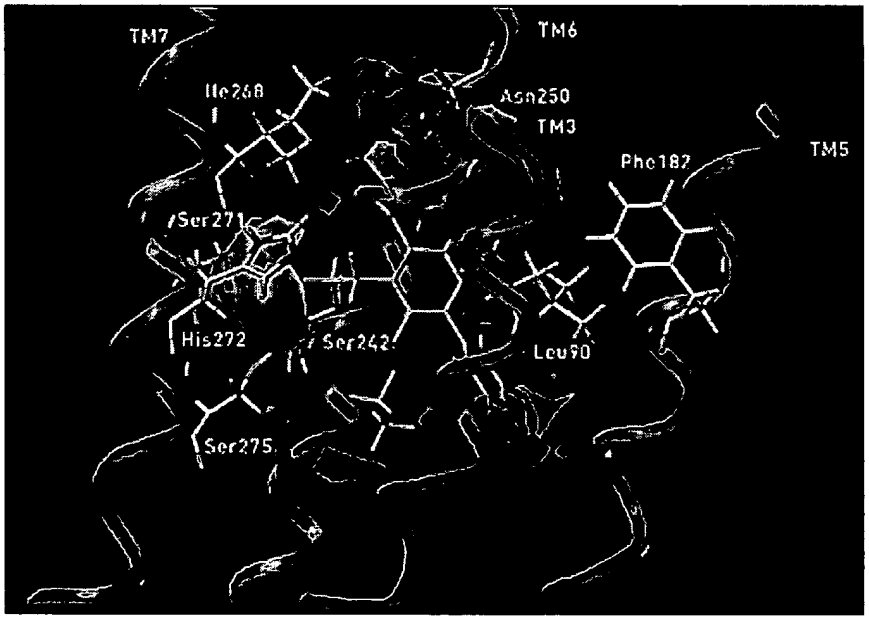
He points out that for most G-protein-coupled receptors (GPCRs), antagonists are the principal targets for drug development, whereas for A_3 the agonists appear to have more potential use as therapeutic agents. "But I wouldn't rule out A_3 antagonists" as potential drugs, he says.

A_3 antagonists have been suggested to be potentially useful in lowering intraocular pressure in glaucoma patients, for instance. This proposal is based on studies on the effects of A_3 ligands on chloride transport in ciliary epithelial cells by Penn professor of physiology and medicine Mortimer M. Civan and coworkers. Civan, Ken Jacobson, and coworkers have filed a joint patent application for use of some of the NIDDK group's antagonists for treatment of glaucoma.

And IJzerman has synthesized some human A_3 antagonists that he believes might be useful as anti-inflammatory agents because they impede the release of allergic mediators from blood cells.

Dov Barak, a molecular modeler from the Israel Institute for Biological Research who is currently on sabbatical in Ken Jacobson's group, notes that the GPCR class to which A_3 receptors belong "is the most prevalent paradigm for signal transduction in nature. Any drug designed to target these receptors will affect major signaling pathways in cells"--suggesting why A_3 studies have been so fruitful.

Barak points out that common structural motifs shared by GPCRs--such as their seven transmembrane a-helices--simplify drug design studies to some extent, because the structure and activity of these receptors are well known. However, the commonality among GPCRs also poses special challenges, he says, in that it makes it more difficult to develop agonists and antagonists with the requisite specificity of action. Only the future will tell to what extent Barak and other researchers succeed in exploiting such opportunities and overcoming such roadblocks as they continue to pursue their efforts to target the A_3 receptor.



COURTESY OF STEFANO MORO AND KEN JACOBSON

WHAT'S UP DOCK Ken Jacobson and coworkers used two molecular modeling methods--receptor homology modeling and comparative molecular field analysis--to study docking of a pyridine antagonist to α-helices of the human A_3 receptor. A_3 receptor amino acids that play a key role in formation of the complex are labeled. Large colored areas are representations

h b c g ce c e ece h

of four types of molecular features that favor enhanced affinity: small groups, yellow; sterically bulky groups, green; and negatively or positively charged structures, red and blue, respectively. TM = transmembrane α-helix.

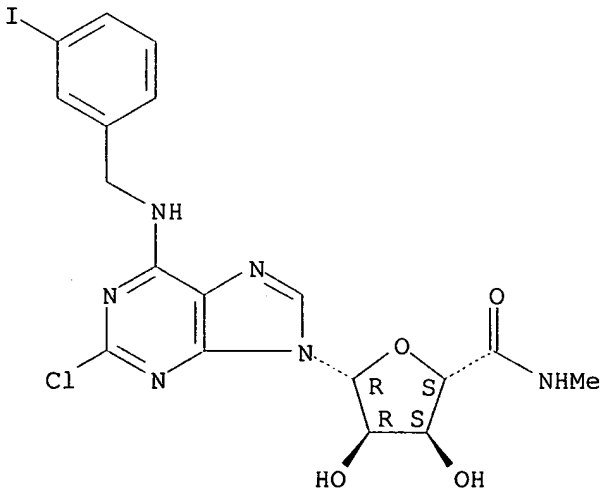
[Previous Story] [Next Story]

Top

Home | Table of Contents | News of the Week | Cover Story
Business | Government & Policy | Science/Technology

h b c g ce c e ece h

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 09:22:38 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 OCT 2002  HIGHEST RN 463296-69-7
DICTIONARY FILE UPDATES:  20 OCT 2002  HIGHEST RN 463296-69-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can tot l16

L16  ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2002 ACS
RN   163042-96-4  REGISTRY
CN   .beta.-D-Ribofuranuronamide, 1-[2-chloro-6-[[(3-iodophenyl)methyl]amino]-
     9H-purin-9-yl]-1-deoxy-N-methyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   2-Chloro-N6-(3-iodobenzyl)adenosine-5'-N-methyluronamide
CN   Cl-IB-MECA
FS   STEREOSEARCH
MF   C18 H18 Cl I N6 O4
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, CHEMCATS, CSCHEM,
       MEDLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.
```



Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43 REFERENCES IN FILE CA (1962 TO DATE)
43 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:163843

REFERENCE 2: 137:136577

REFERENCE 3: 137:88436

REFERENCE 4: 136:380449

REFERENCE 5: 136:319688

REFERENCE 6: 136:273473

REFERENCE 7: 136:272934

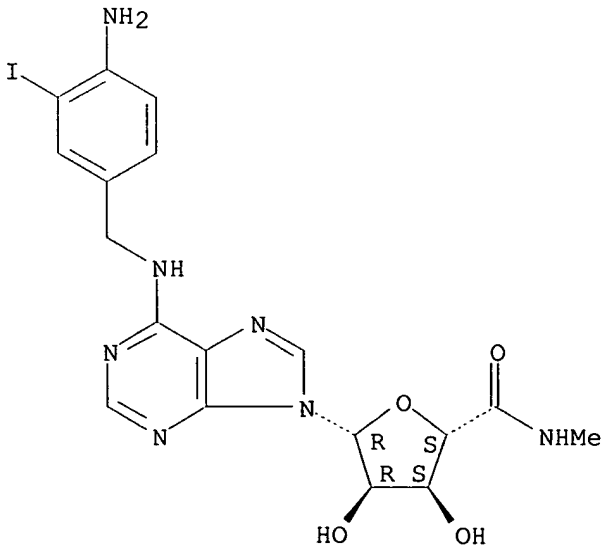
REFERENCE 8: 136:257615

REFERENCE 9: 136:242084

REFERENCE 10: 136:161304

L16 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN **152918-27-9** REGISTRY
CN .beta.-D-Ribofuranuronamide, 1-[6-[[(4-amino-3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AB-MECA
FS STEREOSEARCH
MF C18 H20 I N7 O4
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

20 REFERENCES IN FILE CA (1962 TO DATE)
20 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:163843

REFERENCE 2: 137:136577

REFERENCE 3: 137:88436

REFERENCE 4: 136:380449

REFERENCE 5: 136:48571

REFERENCE 6: 134:231860

REFERENCE 7: 133:261543

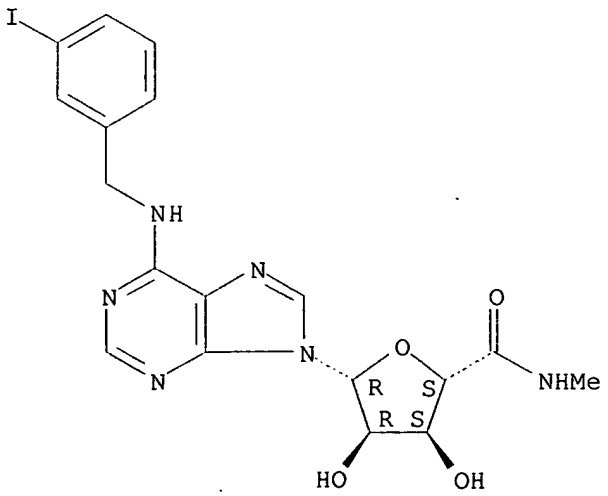
REFERENCE 8: 130:20187

REFERENCE 9: 130:10309

REFERENCE 10: 129:228699

L16 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN **152918-18-8** REGISTRY
CN .beta.-D-Ribofuranuronamide, 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN IB-MECA
CN N6-(3-Iodobenzyl)adenosine-5'-N-methyluronamide
FS STEREOSEARCH
DR 215462-30-9
MF C18 H19 I N6 O4
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CSCHEM, MEDLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

75 REFERENCES IN FILE CA (1962 TO DATE)
75 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:163843

REFERENCE 2: 137:136577

REFERENCE 3: 137:103775

REFERENCE 4: 137:88436

REFERENCE 5: 137:57230

REFERENCE 6: 136:380449

REFERENCE 7: 136:365554

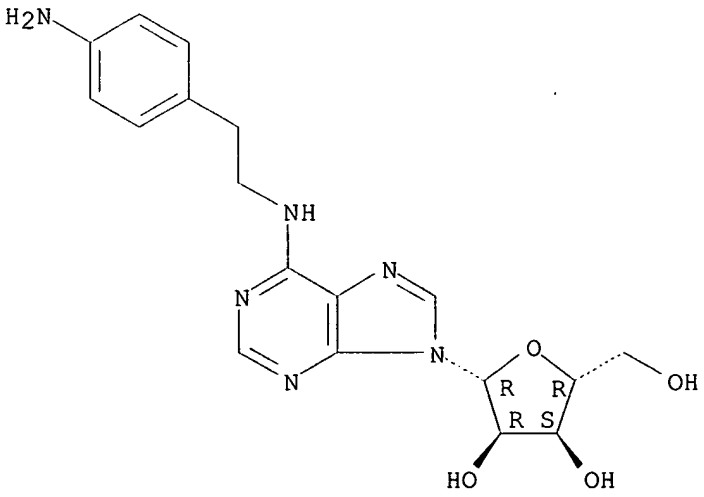
REFERENCE 8: 136:350750

REFERENCE 9: 136:161304

REFERENCE 10: 136:145239

L16 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN **89705-21-5** REGISTRY
CN Adenosine, N-[2-(4-aminophenyl)ethyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN N6-[2-(4-Aminophenyl)ethyl]adenosine
FS STEREOSEARCH
MF C18 H22 N6 O4
LC STN Files: BIOTECHNO, CA, CAPLUS, CHEMCATS, EMBASE, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

44 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

44 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:163843

REFERENCE 2: 137:135364

REFERENCE 3: 137:88436

REFERENCE 4: 136:80176

REFERENCE 5: 134:65798

REFERENCE 6: 133:261543

REFERENCE 7: 133:232652

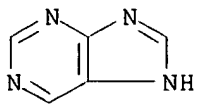
REFERENCE 8: 133:182707

REFERENCE 9: 133:54017

REFERENCE 10: 132:161113

=> d ide can l17

L17 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **120-73-0** REGISTRY
CN 1H-Purine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Purine (6CI, 8CI)
OTHER NAMES:
CN .beta.-Purine
CN 3,5,7-Triazaindole
CN 6H-Imidazo[4,5-d]pyrimidine
CN 7H-Purine
CN 9H-Purine
CN Isopurine
FS 3D CONCORD
DR 273-25-6, 273-26-7, 111055-93-7
MF C5 H4 N4
CI COM, RPS
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3895 REFERENCES IN FILE CA (1962 TO DATE)
2282 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3898 REFERENCES IN FILE CAPLUS (1962 TO DATE)

74 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:253087

REFERENCE 2: 137:247549

REFERENCE 3: 137:244250

REFERENCE 4: 137:242623

REFERENCE 5: 137:242164

REFERENCE 6: 137:241829

REFERENCE 7: 137:229703

REFERENCE 8: 137:228925

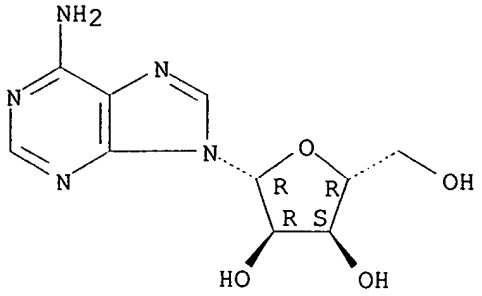
REFERENCE 9: 137:228174

REFERENCE 10: 137:214248

=> d ide can l18

L18 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **58-61-7** REGISTRY
CN Adenosine (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .beta.-Adenosine
CN .beta.-D-Adenosine
CN .beta.-D-Ribofuranose, 1-(6-amino-9H-purin-9-yl)-1-deoxy-
CN .beta.-D-Ribofuranoside, adenine-9
CN 9-.beta.-D-Ribofuranosyl-9H-purin-6-amine
CN 9-.beta.-D-Ribofuranosyladenine
CN 9H-Purin-6-amine, 9-.beta.-D-ribofuranosyl-
CN A
CN Adenine riboside
CN Adenocard
CN Adenoscan
CN Adrekar
CN Boniton
CN D-Adenosine
CN Myocol
CN Nucleocardyl
CN Riboadenosine
CN Sandesin
FS STEREOSEARCH
DR 46946-45-6, 46969-16-8
MF C10 H13 N5 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

17531 REFERENCES IN FILE CA (1962 TO DATE)
933 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
17548 REFERENCES IN FILE CAPLUS (1962 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:245439

REFERENCE 2: 137:245108

REFERENCE 3: 137:243833

REFERENCE 4: 137:243532

REFERENCE 5: 137:243504

REFERENCE 6: 137:242467

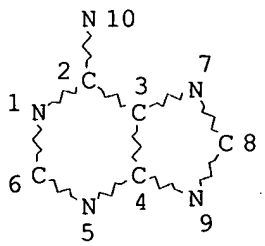
REFERENCE 7: 137:241969

REFERENCE 8: 137:232846

REFERENCE 9: 137:230920

REFERENCE 10: 137:230359

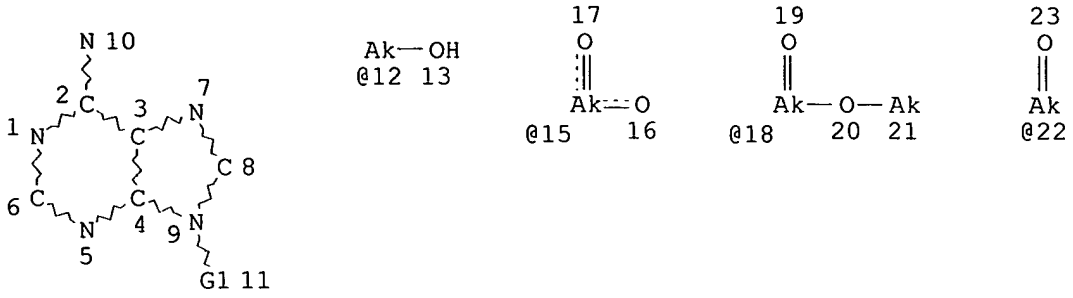
=> d sta que
L44 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L46 96506 SEA FILE=REGISTRY SSS FUL L44
L63 STR



Ak—CN
24 25

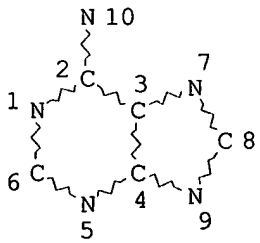
VAR G1=AK/12/15/18/22
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 6
CONNECT IS M1 RC AT 10
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L66 39 SEA FILE=REGISTRY SUB=L46 SSS FUL L63
L67 0 SEA FILE=REGISTRY SUB=L66 CSS FUL L63

100.0% PROCESSED 39 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

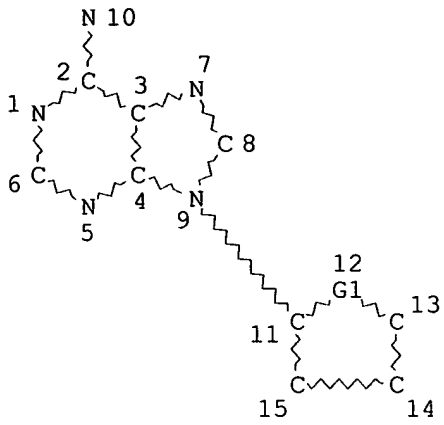
=> d sta que l62
L44 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 1
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L46 96506 SEA FILE=REGISTRY SSS FUL L44
L56 STR



VAR G1=O/S/C
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 6
CONNECT IS M1 RC AT 10
CONNECT IS M1 RC AT 13
CONNECT IS M1 RC AT 14
CONNECT IS M1 RC AT 15
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L58 69707 SEA FILE=REGISTRY SUB=L46 CSS FUL L56
L62 26799 SEA FILE=REGISTRY ABB=ON PLU=ON L46 NOT L58

=> d his

(FILE 'HOME' ENTERED AT 08:04:43 ON 21 OCT 2002)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:05:03 ON 21 OCT 2002
E FISHMAN P/AU
L1 86 S E3-E6,E15
E CAT FITE/PA,CS
E CAT-FITE/PA,CS
E CAN FITE/PA,CS
L2 7 S E5-E10
L3 88 S L1,L2
L4 34 S AB MECA
L5 139 S IB MECA
L6 40 S CL IB MECA
E ADENOSINE RECEPTOR/CT
L7 341 S E10
E A3RAG
L8 707 S ADENOSIN?(L)A3(L)RECEPTOR
E ADENOSINE RECEPTOR/CT
E E5+ALL
L9 261 S E8,E17
L10 280 S E7(L)AGONIST

```
L11         4518 S ADENOSIN?(L)RECEPTOR(L)AGONIST
L12          429 S ADENOSIN?(L)RECEPTOR(L)AGONIST(L)A3
L13           15 S L3 AND L4-L12
L14           41 S N6 2 4 AMINOPHENYL ETHYLADENOSINE
L15            0 S L3 AND L14

     FILE 'REGISTRY' ENTERED AT 08:14:57 ON 21 OCT 2002
L16            4 S 89705-21-5 OR 152918-27-9 OR 152918-18-8 OR 163042-96-4
L17            1 S 120-73-0
L18            1 S 58-61-7
L19            0 S (89705-21-5 OR 152918-27-9 OR 152918-18-8 OR 163042-96-4)/CRN

     FILE 'HCAPLUS' ENTERED AT 08:17:55 ON 21 OCT 2002
L20          138 S L16
L21           25 S 2 CHLORO N6 3 IODOBENZYL ADENOSINE 5 N METHYLURONAMIDE
L22           48 S N6 3 IODOBENZYL ADENOSINE 5 N METHYLURONAMIDE
L23            9 S N6 2 4 AMINOPHENYL ETHYL ADENOSINE
L24            5 S L3 AND L20-L23
L25           15 S L13,L24
L26           12 S L25 AND A3
L27            3 S L25 NOT L26
L28           12 S CI IB MECA
L29           56 S A3AR
L30            4 S L3 AND L28,L29
L31            0 S L30 NOT L26
L32           12 S L26,L30
L33           76 S L3 NOT L32
                 SEL RN L32

     FILE 'REGISTRY' ENTERED AT 08:21:05 ON 21 OCT 2002
L34          129 S E1-E129
L35          100 S L34 AND 333.446/RID
L36           96 S L35 NOT L16
L37           94 S L36 NOT L17,L18

     FILE 'HCAPLUS' ENTERED AT 08:25:19 ON 21 OCT 2002
                 SET SMARTSELECT ON
L38          SEL L33 1- RN :      78 TERMS
                 SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 08:25:21 ON 21 OCT 2002
L39           78 S L38
L40            4 S L39 AND 333.446/RID NOT L35
L41            4 S L40 NOT L17,L18
L42           98 S L37,L41
L43       181680 S 333.446/RID
L44              STR
L45           50 S L44 SAM
L46        96506 S L44 FUL
L47        89542 S L46 NOT SQL/FA
L48        87423 S L47 NOT (MXS OR PMS)/CI
L49              STR L44
L50              STR L49
L51           50 S L50 SAM SUB=L46
L52           74 S L46 AND L34,L39
L53           69 S L52 NOT L16,L17,L18
L54              STR L50
L55            0 S L54 CSS SAM SUB=L46
L56              STR L44
L57           50 S L56 CSS SAM SUB=L46
L58        69707 S L56 CSS FUL SUB=L46
L59              STR L56
L60        47546 S L59 FUL SUB=L58
```

```
L61        22161 S L58 NOT L60
L62        26799 S L46 NOT L58
L63              STR L56
L64              0 S L63 CSS SAM SUB=L46
L65              1 S L63 SAM SUB=L46
L66             39 S L63 FUL SUB=L46
L67              0 S L63 CSS FUL SUB=L66

     FILE 'REGISTRY' ENTERED AT 09:22:38 ON 21 OCT 2002
L68        26780 S L62 NOT L42

     FILE 'HCAPLUS' ENTERED AT 09:28:15 ON 21 OCT 2002

     FILE 'REGISTRY' ENTERED AT 09:28:29 ON 21 OCT 2002
L69              3 S L42 AND CAMP
L70             95 S L42 NOT L69
L71             94 S L70 NOT 58-55-9
L72             93 S L71 NOT 118-00-3
L73             84 S L72 NOT GUANOS?
L74             47 S L73 AND L58
L75             37 S L73 NOT L74
L76             19 S L46 AND L75
L77             66 S L74,L76
                   SAV L77 YOUNG832/A

     FILE 'HCAPLUS' ENTERED AT 09:32:33 ON 21 OCT 2002
L78         1646 S L77
L79        39353 S L62
L80         1135 S L4-L10,L12,L14,L20-L23
L81         2556 S L78,L80
L82        41743 S L79,L81
L83           24 S L82 AND NATURAL KILLER(L)CELL
L84           16 S L82 AND NK(L)CELL
L85           27 S L83,L84
                   E LYMPHOCYTE/CT
L86        11227 S E32-E34,E40-E41
L87           49 S E65
L88           53 S E83
L89           21 S L82 AND L86-L88
L90           29 S L85,L89
L91            6 S L90 AND L81
L92          230 S L4-L6,L20-L23
L93            0 S L92 AND ((NATURAL KILLER OR NK)(L)CELL OR L86-L88)
L94           30 S L92 AND (?NEOPLAS? OR ?CANCER? OR ?CARCIN? OR ?TUMOR? OR ?MAL
L95            7 S L3 AND L92
L96           15 S L3 AND L81
L97            8 S L96 NOT L95
L98           15 S L32,L95-L97
L99           15 S L98 AND L1-L15,L20-L33,L78-L98
L100           9 S L99 AND L17,L18
L101          15 S L99,L100
L102          25 S L94 NOT L101

     FILE 'REGISTRY' ENTERED AT 09:41:35 ON 21 OCT 2002

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 09:41:57 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 21 Oct 2002 VOL 137 ISS 17
FILE LAST UPDATED: 20 Oct 2002 (20021020/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

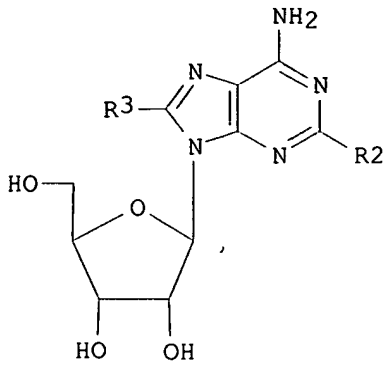
=> d all tot l101

L101 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:695995 HCAPLUS
DN 137:217181
TI Preparation of C2,8-di-substituted nucleoside derivatives as **adenosine receptor agonists**
IN Van Tilburg, Erica; Ijzerman, Ad
PA Universiteit Leiden, Neth.; **Can-Fite Biopharma Ltd.**
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H019-16
ICS A61K031-70; A61P007-02
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002070534	A1	20020912	WO 2002-IL161	20020303

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2001-5335 A 20010303
OS MARPAT 137:217181
GI



I

AB The present invention pertains to novel C2,8-disubstituted **adenosine** derivs. I, wherein R2 and R3, which may be the same or different, represent a lower alkyl, lower alkenyl, lower alkynyl, lower (ar)alkyl, lower alkoxy, lower alkylidenehydrazino, cyano, acetoamino, halogen, a group of the general formula NR4R5 wherein R4 and R5 represent, independently, a hydrogen atom, lower alkyl or (ar)alkyl group, with the proviso that: (i) when R2 represents NH2, R3 does not represent a halogen, alkyl or alkoxy; (ii) when R2 represents an alkylthio, R3 does not represent an alkyl; (iii) when R2 represents a halogen or alkyl, R3 does not represent, resp., a halogen or alkyl., which are found to be potent **adenosine receptor agonist**, particularly for the A2A **receptor**. Further provided by the invention is a process for the prepn. of such **adenosine** derivs. and pharmaceutical compns. comprising said compds. Thus, 2-iodo-8-methylaminoadenosine was prepd. and tested in rats as **adenosine receptor agonist**. All compds. prepd. were tested in radio-ligand binding assays to det. their affinities for the **adenosine** A1 **receptor** in rat brain cortex, the A2A **receptor** in rat striatum and the human **A3 receptor** as expressed in HEK 293 cells.

ST human **adenosine receptor agonist** nucleoside prepn nucleoside

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2A; prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT Human
(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT Nucleosides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT **35109-88-7**
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)

(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT **90596-73-9P 181873-18-7P 457061-01-7P**
457061-02-8P 457061-03-9P 457061-04-0P
457061-05-1P 457061-06-2P 457061-07-3P
457061-08-4P 457061-09-5P 457061-10-8P
457061-11-9P 457061-12-0P 457061-13-1P
457061-14-2P 457061-15-3P 457061-16-4P
457061-17-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT 693-02-7, 1-Hexyne
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

IT 37490-22-5P **94042-04-3P 457060-99-0P**
457061-00-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of C2,8-disubstituted nucleoside derivs. as **adenosine receptor agonists**)

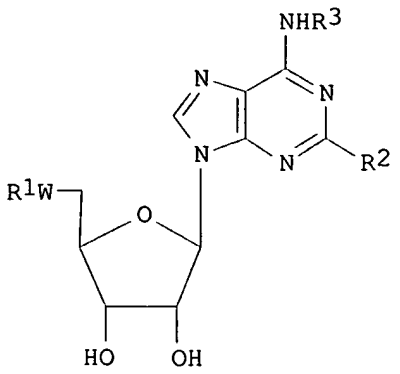
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) E; WO 0078777 A 2000 HCAPLUS
(2) Linden, J; US 5877180 A 1999 HCAPLUS
(3) Ratsep, P; NUCLEOSIDES NUCLEOTIDES 1990, V9(8), P1001 HCAPLUS
(4) Roelen, H; JOURNAL OF MEDICINAL CHEMISTRY 1996, V39, P1463 HCAPLUS
(5) Suehiro, H; US 3968102 A 1976 HCAPLUS

L101 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:695993 HCAPLUS
DN 137:217179
TI Preparation of C2,5'-disubstituted and N6,C2,5'-tri-substituted nucleosides as **adenosine receptor agonists**
IN Van Tilburg, Erica; Ijzerman, Ad
PA Universiteit Leiden, Neth.; **Can-Fite Biopharma Ltd.**
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H019-00
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002070532	A2	20020912	WO 2002-IL160	20020303

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2001-5337 A 20010303
OS MARPAT 137:217179
GI



I

AB The present invention concerns novel C2,5'-disubstituted and N6',C2,5'-trisubstituted **adenosine** derivs. I wherein, W represents an oxygen or sulfur atom; R1 represents a lower alkyl or lower cycloalkyl; R2 represents a halogen, lower alkenyl, lower alkynyl or lower alkylidenehydrazino; R3 represents lower alkyl, lower cycloalkyl, (ar)alkyl, aryl or anilide; said cycloalkyl aryl and (ar)alkyl may be substituted with one or more substituent selected from halogen, hydroxy, hydroxyalkyl; or a salt of said compd. and their different uses. These **adenosine** derivs. were found to be potent **adenosine receptor agonists** and thus are of a therapeutic value in the treatment and prophylaxis of diseases and disorders affected by **adenosine receptor agonists**. Thus, 5'-deoxy--2-iodo-5'-ethylthioadenosine was prepd. and tested in vivo as human **adenosine receptor agonist**. The ability of title compds. to either stimulate cAMP prodn. through human **adenosine** A2A **receptors** expressed in CHO cells or inhibit the cAMP prodn. in human **adenosine A3 receptors** expressed in HEK 293 cells was assessed.

ST human **adenosine receptor** nucleoside prepn **agonist** prophylaxis human

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2A; prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**
)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**
)

IT Drugs
Human
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT Nucleosides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as

adenosine receptor agonists)

IT 60-92-4, CAMP
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT **398139-03-2P 398139-04-3P 398139-05-4P**
398139-06-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT **15763-11-8P 20649-45-0P 144348-17-4P**
362046-25-1P 362046-26-2P 362046-29-5P
362046-31-9P 362046-32-0P 362046-33-1P
362046-34-2P 362046-35-3P 362046-36-4P
362046-37-5P 362046-38-6P 362046-39-7P
362046-40-0P 362046-41-1P 362046-42-2P
362046-43-3P 362046-44-4P 398139-07-6P
398139-08-7P 398139-09-8P 398139-11-2P
398139-17-8P 398139-18-9P 398139-19-0P
398139-20-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT 50-69-1, D-Ribose 74-93-1, Methanethiol, reactions 75-08-1, Ethanethiol 75-33-2, Isopropylthiol 107-03-9, Propylthiol 110-46-3, Isopentyl nitrite 118-00-3, Guanosine, reactions 121-69-7, N,N-Dimethylaniline, reactions 590-86-3, Isovaleraldehyde 693-02-7, 1-Hexyne 1003-03-8, Cyclopentylamine 3718-88-5 4099-85-8, Methyl 2,3-O-isopropylidene-.beta.-D-ribofuranoside **35109-88-7**, 2-Iodoadenosine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

IT 6748-97-6P 7770-26-5P 21017-09-4P 33985-44-3P **90596-73-9P**
114405-47-9P 142646-57-9P 169190-87-8P 188579-98-8P 188580-00-9P
223756-62-5P 362046-17-1P 362046-18-2P 362046-19-3P 362046-20-6P
362046-21-7P 362046-22-8P 362046-23-9P 362046-24-0P 398138-88-0P
398138-89-1P 398138-90-4P 398138-92-6P 398138-93-7P 398138-94-8P
398138-95-9P 398138-96-0P 398138-97-1P 398138-98-2P 398138-99-3P
398139-00-9P 398139-01-0P 398139-02-1P **398139-12-3P**
398139-13-4P 398139-15-6P 398139-16-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of C2,5'-disubstituted and N6,C2,5'-substituted nucleosides as **adenosine receptor agonists**)

L101 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:638281 HCAPLUS
DN 137:163843
TI Adenosine receptor ligands for the modulation of glycogen synthase kinase 3.beta. (GSK-3.beta.) activity, and therapeutic uses
IN **Fishman, Pnina**; Khalili, Kamel
PA Israel
SO U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-522
ICS A61K031-52; A61K031-7076

NCL 514046000
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002115635	A1	20020822	US 2001-788477	20010221
	WO 2002066020	A2	20020829	WO 2002-IL134	20020221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-788477 A 20010221

AB A method is provided for a therapeutic treatment, comprising administering an effective amt. of an active agent for achieving a therapeutic effect, the therapeutic effect comprising modulating GSK-3.beta. activity in cells and the active agent being an **adenosine** A1 **receptor** ligand, an **adenosine** A2 **receptor** ligand, an **adenosine A3 receptor** ligand, or a combination thereof.

ST adenosine receptor ligand glycogen synthase kinase modulation therapeutic; GSK3beta modulation adenosine receptor ligand therapeutic

IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3; adenosine receptor** ligand for modulation of GSK-3.beta., and therapeutic use)

IT Animal cell line
(B-16-F10; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D1; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Animal cell line
(HT-116; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Lef/Tcf; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Signal transduction, biological
(Wnt pathway; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

IT Alopecia
Antidiabetic agents
Drug delivery systems
Human
Mental disorder
Nervous system agents
Psychotropics

(adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-myc; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Intestine, **neoplasm**
(colon, **carcinoma**; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Animal cell
Nervous system
(degeneration; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Nervous system
(disease, neurotraumatic disorders; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Diabetes mellitus
(non-insulin-dependent; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Drug delivery systems
(oral; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT Catenins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT **Melanoma**
(.beta.-catenin expression in; adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT 443900-95-6, Glycogen synthase kinase 3.beta.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)
IT 14114-46-6, DMPX **36396-99-3 38594-96-6**
41552-82-3, N6-Cyclopentyladenosine **89705-21-5**
96865-92-8 102146-07-6 **120442-40-2 152918-18-8**
152918-27-9 163042-96-4 183721-15-5 205928-53-6D, derivs. 212329-37-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine receptor ligand for modulation of GSK-3.beta., and therapeutic use)

L101 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:539536 HCAPLUS
DN 137:88436
TI Use of an **adenosine A3 receptor agonist** for inhibition of viral replication
IN **Fishman, Pnina**; Khalili, Kamel
PA **Can-Fite Biopharma Ltd., Israel**
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-52
ICS A61P031-18
CC 1-5 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002055085	A2	20020718	WO 2002-IL28	20020113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2001-261659P P 20010116
OS MARPAT 137:88436
AB The invention discloses the use of **agonists** of the **adenosine receptor** system for inhibiting viral replication in cells. In particular, the invention provides a compn. and method for inhibiting viral replication in cells, the method comprising presenting to the cells an effective amt. of an **adenosine A3 receptor agonist**. The invention is particularly useful, for although not limited to, inhibiting the replication of HIV virus in human cells.
ST **adenosine A3 receptor agonist** virucide; HIV virucide **adenosine A3 receptor agonist**
IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3; adenosine A3 receptor agonist** for inhibition of viral replication)
IT Anti-AIDS agents
Antiviral agents
Astrocyte
Drug delivery systems
Human
Human immunodeficiency virus
Human immunodeficiency virus 1
(**adenosine A3 receptor agonist** for inhibition of viral replication)
IT Nucleotides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; **adenosine A3 receptor agonist** for inhibition of viral replication)
IT Neuroglia
(microglia; **adenosine A3 receptor agonist** for inhibition of viral replication)
IT **120-73-0D**, Purine, derivs. **89705-21-5** **152918-14-4D**, derivs. **152918-18-8**, **IB-MECA 152918-27-9**, **AB-MECA** **163042-96-4**, **Cl-IB-MECA**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adenosine A3 receptor agonist** for inhibition of viral replication)

L101 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:471968 HCAPLUS
TI Evidence for involvement of Wnt signaling pathway in **IB-MECA** mediated suppression of **melanoma** cells
AU **Fishman, Pnina**; Madi, Lea; Bar-Yehuda, Sara; Barer, Faina; Del Valle, Luis; Khalili, Kamel
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Sackler Faculty of Medicine, Rabin Medical Center, Tel Aviv University, Petach-Tikya, 49100, Israel
SO Oncogene (2002), 21(25), 4060-4064
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group

DT Journal
LA English
CC 1 (Pharmacology)
AB The **A3 adenosine receptor, A3AR,** belongs to the family of Gi proteins, which upon induction, suppresses the formation of cAMP and its downstream effectors. Recent studies have indicated that activation of **A3AR** by its **agonist, IB-MECA**, results in growth inhibition of **malignant** cells. Here we demonstrate the ability of **IB-MECA** to decrease the levels of protein kinase A, a downstream effector of cAMP, and protein kinase B/Akt in **melanoma** cells. Examn. of glycogen synthase kinase 3.beta., GSK-3.beta., whose phosphorylation is controlled by protein kinase A and B, showed a substantial decrease in the levels of its phosphorylated form and an increase in total GSK-3.beta. levels in **IB-MECA** treated **melanoma** cells. This observation suggests that the treatment of cells with **IB-MECA** augments the activity of GSK-3.beta. in the cells. Evaluation of .beta.-catenin, a key component of Wnt signaling pathway which, upon phosphorylation by GSK-3.beta. rapidly ubiquitinates, showed a substantial decrease in its level after **IB-MECA** treatment. Accordingly, the level of .beta.-catenin responsive cell growth regulatory genes including c-myc and cyclin D1 was severely declined upon treatment of the cells with **IB-MECA**. These observations which link cAMP to the Wnt signaling pathway provide mechanistic evidence for the involvement of Wnt pathway via its key elements GSK-3.beta. and .beta.-catenin in the anti-**tumor** activity of **A3AR agonists**.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Ausubel, F; Current Protocols in Molecular Biology 1989, P342
(2) Bar-Yehuda, S; Neoplasia 2001, V3, P125 HCAPLUS
(3) Bonvini, P; Biochim Biophys Acta 2000, V1495, P308 HCAPLUS
(4) Caballero, O; Invest Ophthalmol Vis Sci 2001, V42, P1679
(5) Cerni, C; Mutat Res 2000, V462, P31 HCAPLUS
(6) Cross, D; Nature 1995, V378, P785 HCAPLUS
(7) Diehl, J; Genes Dev 1998, V12, P3499 HCAPLUS
(8) D'Agnano, I; Oncogene 2001, V20, P2814 HCAPLUS
(9) Fang, X; Proc Natl Acad Sci USA 2000, V97, P11960 HCAPLUS
(10) Ferkey, D; Dev Biol 2000, V225, P471 HCAPLUS
(11) Filippa, N; Mol Cell Biol 1999, V19, P4989 HCAPLUS
(12) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(13) Fishman, P; Eur J Cancer 2000, V36, P1452 HCAPLUS
(14) Fishman, P; Exp Cell Res 2001, V269, P230 HCAPLUS
(15) Gan, D; Oncogene 2001, V20, P4864 HCAPLUS
(16) Li, M; Mol Cell Biol 2000, V20, P9356 HCAPLUS
(17) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(18) McEwen, D; Curr Biol 2000, V10, P562
(19) Miracco, C; Int J Cancer 2000, V88, P411 HCAPLUS
(20) Morin, P; Bioessays 1999, V21, P1021 MEDLINE
(21) Moule, S; J Biol Chem 1997, V272, P7713 HCAPLUS
(22) Novak, A; Cell Mol Life Sci 1999, V56, P523 HCAPLUS
(23) Ohana, G; J Cellular Physiol 2000, V186, P19
(24) Robbins, P; Exp Med 1996, V183, P1185 HCAPLUS
(25) Sable, C; FEBS Lett 1997, V409, P253 HCAPLUS
(26) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(27) Zhao, Z; Biochim Biophys Acta 2000, V1500, P280 HCAPLUS

L101 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:469221 HCAPLUS
TI **A3 adenosine receptor** as a target for **cancer** therapy
AU **Fishman, Pnina**; Bar-Yehuda, Sara; Madi, Lea; Cohn, Ilan
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical

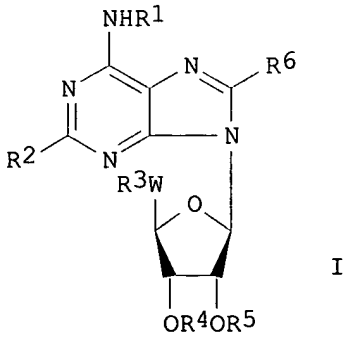
Research Center, Rabin Medical Center, Tel-Aviv University, Petach Tikva, 49100, Israel
SO Anti-Cancer Drugs (2002), 13(5), 437-443
CODEN: ANTDEV; ISSN: 0959-4973
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1 (Pharmacology)
AB Targeting the **A3 adenosine receptor** (**A3AR**) by **adenosine** or a synthetic **agonist** to this **receptor** (**IB-MECA** and **CI-IB-MECA**) results in a differential effect on **tumor** and on normal cells. Both the **adenosine** and the **agonists** inhibit the growth of various **tumor** cell types such as **melanoma**, colon or prostate **carcinoma** and lymphoma. This effect is specific and is exerted on **tumor** cells only. Moreover, exposure of peripheral blood mononuclear cells to **adenosine** or the **agonists** leads to the induction of granulocyte colony stimulating factor (G-CSF) prodn. When given orally to mice, the **agonists** suppress the growth of **melanoma**, colon and prostate **carcinoma** in these animals, while inducing a myeloprotective effect via the induction of G-CSF prodn. The de-regulation of the Wnt signaling pathway was found to be involved in the **anticancer** effect. **Receptor** activation induces inhibition of adenylyl cyclase with a subsequent decrease in the level of protein kinase A and protein kinase B/Akt leading to activation of glycogen synthase kinase-3.beta., a key element in the Wnt pathway. The oral bioavailability of the synthetic **A3AR agonists**, and their induced systemic **anticancer** and myeloprotective effect, renders them potentially useful in three different modes of treatment: as a standalone **anticancer** treatment, in combination with chemotherapy to enhance its therapeutic index and myelprotection. It is evident that use of the **A3AR agonist** for increasing the therapeutic index of chemotherapy may also invariably give rise to myeloprotection and vice versa. The **A3AR agonists** are thus a promising new class of agents for **cancer** therapy.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bar-Yehuda, S; Clin Exp Metast 1999, V17, P531 HCAPLUS
(2) Bar-Yehuda, S; Neoplasia 2001, V3, P125 HCAPLUS
(3) Bowlin, T; Cell Mol Biol 1997, V43, P345 HCAPLUS
(4) Djaldetti, M; Clin Exp Metast 1996, V14, P189 HCAPLUS
(5) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(6) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(7) Fishman, P; Eur J Cancer 2000, V36, P1452 HCAPLUS
(8) Fishman, P; J Cell Physiol 2000, V183, P393 HCAPLUS
(9) Fishman, P; Oncogene, in press 2002
(10) Gessi, S; Br J Pharmacol 2001, V134, P116 HCAPLUS
(11) Jacobson, K; Drugs Fut 1995, V20, P689
(12) Jacobson, K; J Biol Chem 2000, V275, P30272 HCAPLUS
(13) Liu, G; Cardiovasc Res 1994, V28, P1057 HCAPLUS
(14) Merighi, S; Br J Pharmacol 2001, V134, P1215 HCAPLUS
(15) Olah, M; Pharmacol Ther 2000, V85, P55 HCAPLUS
(16) Palmer, T; Mol Pharmacol 1997, V52, P632 HCAPLUS
(17) Palmer, T; Mol Pharmacol 2000, V57, P539 HCAPLUS
(18) Poulsen, S; Bioorg Med Chem 1998, V6, P619 HCAPLUS
(19) Shneyvays, V; J Mol Cell Cardiol 2001, V33, P1249 HCAPLUS
(20) Suh, B; Br J Pharmacol 2001, V134, P132 HCAPLUS
(21) Trincavelli, M; J Neurochem 2000, V75, P1493 HCAPLUS
(22) Von Lubitz, D; Ann NY Acad Sci 2001, V939, P85 HCAPLUS
(23) Zhao, Z; Microvasc Res 2002, V63, P61 HCAPLUS

L101 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2002 ACS

AN 2002:241343 HCAPLUS
DN 136:257289
TI Pharmaceutical use of adenosine agonists for inducing bone marrow cell proliferation
IN **Fishman, Pnina**; Cohn, Ilan
PA Israel
SO U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 782,259.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-7076
NCL 514046000
CC 1-12 (Pharmacology)
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002037871	A1	20020328	US 2001-871963	20010604
	WO 2000040251	A1	20000713	WO 2000-IL14	20000107
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001031742	A1	20011018	US 2001-782259	20010214
PRAI	IL 1999-127947	A	19990107		
	WO 2000-IL14	W	20000107		
	US 2001-700744	A2	20010109		
	US 2001-782259	A2	20010214		

OS MARPAT 136:257289
GI



I

AB The present invention relates to a method for inducing proliferation of the hematopoietic system, in particular, of bone marrow cells, comprising administering to a subject an effective amt. of an **adenosine** A1 **receptor agonist**. The method of the invention may be utilized in a variety of clin. situations where such proliferation is therapeutically beneficial. The active ingredient within the pharmaceutical compn. of the invention may be a compd. of general formula I (R1 represents a lower alkyl, substituted or unsubstituted cycloalkyl, hydroxy or hydroxyalkyl, etc.; R2 represents hydrogen, halogen, substituted or unsubstituted lower alkyl or alkenyl, lower haloalkyl or

alkenyl cyano, etc.; W represents the group -OCH2-, -NHCH2-, -SCH2- or -NH(C:O)-; R3, R4 and R5 represent independently hydrogen, lower alkyl or lower alkenyl, branched or unbranched C1-C12alkanoyl, benzoyl or substituted benzoyl, etc.; and R6 represents a hydrogen or halogen atom) or any other compd. or substance which specifically binds to and/or activates the A1 **adenosine receptor** and acts as an **agonist** to the **receptor**'s natural ligand.

ST **adenosine** A1 **agonist** bone marrow cell proliferation induction; leukopenia prevention **adenosine** A1 **receptor agonist**; hematopoiesis induction **adenosine** A1 **receptor agonist**

IT Purinoceptor agonists
(A1; adenosine agonists for inducing bone marrow cell proliferation)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; **adenosine agonists** for inducing bone marrow cell proliferation)

IT Bone marrow
Cell proliferation
Drug interactions
Leukocytopenia
(adenosine agonists for inducing bone marrow cell proliferation)

IT Toxicity
(drug, leukopenia in; adenosine agonists for inducing bone marrow cell proliferation)

IT Hematopoiesis
(induction of; adenosine agonists for inducing bone marrow cell proliferation)

IT Antipsychotics
Antitumor agents
Chemotherapy
Radiotherapy
Tranquilizers
(leukopenia from; adenosine agonists for inducing bone marrow cell proliferation)

IT Neoplasm
(leukopenia in; adenosine agonists for inducing bone marrow cell proliferation)

IT Agranulocytosis
(neutropenia; adenosine agonists for inducing bone marrow cell proliferation)

IT **58-61-7D**, Adenosine, derivs. **36396-99-3**, Adenosine, N-cyclohexyl- **37739-05-2**, 2-Chloro-N6-cyclopentyladenosine **41552-82-3**, N6-Cyclopentyladenosine **204512-90-3**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine agonists for inducing bone marrow cell proliferation)

IT 143011-72-7, G-CSF
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction of; adenosine agonists for inducing bone marrow cell proliferation)

IT 50-18-0, Cyclophosphamide
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leukopenia from; adenosine agonists for inducing bone marrow cell proliferation)

L101 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:763522 HCAPLUS
DN 135:283233
TI Pharmaceutical use of adenosine agonists for inducing bone marrow cell proliferation

IN **Fishman, Pnina**; Cohn, Ilan
PA Israel
SO U.S. Pat. Appl. Publ., 10 pp., Cont.-in-part of U.S. Ser. No. 700,744.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-7105
NCL 514045000
CC 1-12 (Pharmacology)
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2001031742	A1	20011018	US 2001-782259	20010214
	WO 2000040251	A1	20000713	WO 2000-IL14	20000107
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002037871	A1	20020328	US 2001-871963	20010604
PRAI	IL 1999-127947	A	19990107		
	WO 2000-IL14	P	20000107		
	US 2001-700744	A2	20010109		
	US 2001-782259	A2	20010214		

OS MARPAT 135:283233
AB A method is provided for inducing proliferation of bone marrow cells in a subject, compromising administering an effective amt. of an **adenosine** A1 **receptor agonist**. Also provided is a method for preventing redn. in level of leukocytes in a subject as a result of a treatment comprising administering to the individual an effective amt. of an **adenosine** A1 **receptor agonist**. In addn., the invention provides a method of treatment of an individual comprising administering to the subject a therapeutic drug in combination with an **adenosine** A1 **receptor agonist**.
ST **adenosine** A1 **agonist** bone marrow cell proliferation induction; leukopenia prevention **adenosine** A1 **receptor agonist**
IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A1; **adenosine agonists** for inducing bone marrow cell proliferation)
IT Antipsychotics
Antitumor agents
Bone marrow
Cell proliferation
Chemotherapy
Drug interactions
Drugs
Leukocytopenia
Radiotherapy
Tranquilizers
(adenosine agonists for inducing bone marrow cell proliferation)
IT Toxicity
(drug; adenosine agonists for inducing bone marrow cell proliferation)
IT Agranulocytosis
(neutropenia; adenosine agonists for inducing bone marrow cell proliferation)

IT 50-18-0, Cyclophosphamide
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine agonists for inducing bone marrow cell proliferation)
IT **58-61-7D**, Adenosine, derivs., biological studies
36396-99-3 37739-05-2, 2-Chloro-N6-cyclopentyladenosine
41552-82-3, N6-Cyclopentyladenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine agonists for inducing bone marrow cell proliferation)
IT 143011-72-7, G-CSF
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenosine agonists for inducing bone marrow cell proliferation)

L101 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:698571 HCAPLUS
DN 136:144762
TI The **A3 Adenosine Receptor** as a New Target for **Cancer** Therapy and Chemoprotection
AU **Fishman, Pnina**; Bar-Yehuda, Sara; Barer, Faina; Madi, Lea; Multani, Asha S.; Pathak, Sen
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Rabin Medical Center, Tel-Aviv University Sackler Faculty of Medicine, Petach-Tikva, 49100, Israel
SO Experimental Cell Research (2001), 269(2), 230-236
CODEN: ECREAL; ISSN: 0014-4827
PB Academic Press
DT Journal
LA English
CC 1-6 (Pharmacology)
AB **Adenosine**, a purine nucleoside, acts as a regulatory mol., by binding to specific G-protein-coupled A1, A2A, A2B, and **A3** cell surface **receptors**. We have recently demonstrated that **adenosine** induces a differential effect on **tumor** and normal cells. While inhibiting in vitro **tumor** cell growth, it stimulates bone marrow cell proliferation. This dual activity was mediated through the **A3 adenosine receptor**. This study showed that a synthetic **agonist** to the **A3 adenosine receptor**, 2-chloro-N6-(3-iodobenzyl)-**adenosine**-5'-N- methyl-uronamide (**Cl-IB-MECA**), at nanomolar concns., inhibited **tumor** cell growth through a cytostatic pathway, i.e., induced an increase no. of cells in the G0/G1 phase of the cell cycle and decreased the telomeric signal. Interestingly, **Cl-IB-MECA** stimulates murine bone marrow cell proliferation through the induction of granulocyte-colony-stimulating factor. Oral administration of **Cl-IB-MECA** to **melanoma**-bearing mice suppressed the development of **melanoma** lung metastases (60.8.+-.6.5% inhibition). In combination with cyclophosphamide, a synergistic anti-**tumor** effect was achieved (78.5.+-.9.1% inhibition). Furthermore, **Cl-IB-MECA** prevented the cyclophosphamide-induced myelotoxic effects by increasing the no. of white blood cells and the percentage of neutrophils, demonstrating its efficacy as a chemoprotective agent. We conclude that **A3 adenosine receptor agonist, Cl-IB-MECA**, exhibits systemic **anticancer** and chemoprotective effects. (c) 2001 Academic Press.
ST chloroiodobenzyladenosinemethyluronamide cyclophosphamide **antitumor** adenosine receptor chemoprotectant cell cycle
IT **Antitumor** agents

Cytoprotective agents
Neutrophil
(**A3 adenosine receptor** as a new target
for **cancer** therapy and chemoprotection)
IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; **A3 adenosine receptor** as a
new target for **cancer** therapy and chemoprotection)
IT Interphase (cell cycle)
(G0-phase; **A3 adenosine receptor** as a new
target for **cancer** therapy and chemoprotection)
IT Interphase (cell cycle)
(G1-phase; **A3 adenosine receptor** as a new
target for **cancer** therapy and chemoprotection)
IT **Antitumor** agents
(lung, metastasis; **A3 adenosine receptor**
as a new target for **cancer** therapy and chemoprotection)
IT **Antitumor** agents
(**melanoma**; **A3 adenosine receptor**
as a new target for **cancer** therapy and chemoprotection)
IT Lung, **neoplasm**
(metastasis, inhibitors; **A3 adenosine**
receptor as a new target for **cancer** therapy and
chemoprotection)
IT Drug interactions
(synergistic; **A3 adenosine receptor** as a
new target for **cancer** therapy and chemoprotection)
IT 50-18-0, Cyclophosphamide **163042-96-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(**A3 adenosine receptor** as a new target
for **cancer** therapy and chemoprotection)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bar-Yehuda, S; Neoplasia 2001, V3, P125 HCAPLUS
(2) Bar-Yehuda, S; Neoplasia 2001, V3, P125 HCAPLUS
(3) Bowlin, T; Cell Mol Biol 1997, V43, P345 HCAPLUS
(4) Brambilla, R; Naunyn-Schmiedeberg's Arch Pharmacol 2000, V361, P225 HCAPLUS
(5) Ceruti, S; Drug Dev Res 1996, V37, P177
(6) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(7) Fishman, P; Eur J Cancer 2000, V36, P1452 HCAPLUS
(8) Fishman, P; J Cell Physiol 2000, V183, P393 HCAPLUS
(9) Heine, B; Br J Ophthalmol 2000, V84, P217 MEDLINE
(10) Ikebuchi, A; Blood 1988, V72, P2007
(11) Itoh, Y; Int J Hematol 1992, V55, P139 MEDLINE
(12) Jacobson, K; Drug Dev Res 1998, V45, P113 HCAPLUS
(13) Kallassy, M; Mol Carcinog 1998, V21, P26 HCAPLUS
(14) Krishan, A; J Cell Biol 1975, V66, P188 MEDLINE
(15) Li, A; Bioconjucate Chem 1999, V10, P667 HCAPLUS
(16) Li, A; J Med Chem 1999, V42, P706 HCAPLUS
(17) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(18) Liu, G; Cardiovasc Res 1994, V28, P1057 HCAPLUS
(19) Multani, A; Anticancer Res 1996, V16, P3435 MEDLINE
(20) Multani, A; Int J Oncol 1999, V15, P423 HCAPLUS
(21) Pathak, S; J Reprod Med 1976, V17, P25 MEDLINE
(22) Ramirez, R; Neoplasia 1999, V1, P42 HCAPLUS
(23) Shneyvays, V; Exp Cell Res 2000, V257, P111 HCAPLUS
(24) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(25) Van Schaick, E; Eur J Pharmacol 1996, V308, P311 HCAPLUS
(26) Von Lubitz, D; Ann NY Acad Sci 1999, V890, P93 HCAPLUS
(27) von Lubitz, D; Eur J Pharmacol 1994, V263, P59 HCAPLUS
(28) Von Lubitz, D; Eur J Pharmacol 1995, V275, P23 HCAPLUS
(29) Wright, W; Nat Med 2000, V8, P849

(30) Yao, Y; Biochem Biophys Res Commun 1997, V232, P317 HCAPLUS

L101 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:383911 HCAPLUS
DN 136:128668
TI Resistance of muscle to tumor metastases: A role for **A3 adenosine receptor agonists**
AU Bar-Yehuda, Sara; Barer, Faina; Volfsson, Lea; **Fishman, Pnina**
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel-Aviv University, Petach Tikva, Israel
SO Neoplasia (New York, NY, United States) (2001), 3(2), 125-131
CODEN: NEOPFL; ISSN: 1522-8002
PB Nature America Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 2, 14, 63
AB Tumor metastases are extremely rare in striated muscles. Lately, we have found that muscle cell conditioned medium (MCM) inhibits the proliferation of various tumor cells while maintaining the growth of normal murine bone marrow cells. This dual activity was confirmed in vivo when the MCM was administered orally, i.e., it inhibited the development of tumor growth in mice and prevented the myelotoxic effects of chemotherapy. **Adenosine** was found to be one of the active components of MCM, inhibiting tumor cell growth while maintaining bone marrow cell proliferation in vitro. **Adenosine** is known to act as an important regulatory mol. through its binding to specific G-protein-assocd. A1, A2a, A2b and **A3** cell surface **receptors**. In distinction from MCM, **adenosine** did not suppress tumor development in mice and was not active as a chemoprotective agent when administered orally or i.v. Thus, the in vivo activity of MCM could not be attributed to **adenosine**. In this study, MCM from which **adenosine** was enzymically removed still retained its dual activity that was also found to be mediated through the **A3 adenosine receptor** (**A3AR**). This result led to the conclusion that natural **agonists** to **A3AR** were responsible for the activity of MCM. We further tested synthetic **agonist** to the **A3AR** and demonstrated that it possessed the same in vitro and in vivo activity profile as MCM. Taken together, muscle cells, in addn. to **adenosine**, secrete natural **agonists** to **A3AR**. These **agonists** are stable nondegradable mols. and may contribute to the systemic anticancer and chemoprotective activity exerted by MCM. This group of mols. may account for the rarity of tumor metastases in muscle.
ST tumor metastasis muscle resistance **adenosine receptor agonist**; anticancer oral muscle cell conditioned medium **adenosine**
IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Antitumor agents
(lung, metastasis; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Antitumor agents
(melanoma; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Lung, neoplasm
(metastasis, inhibitors; role for **A3 adenosine receptor agonists** in muscle resistance to tumor

metastases)
IT Antitumor agents
(metastasis; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Drug delivery systems
(oral; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Muscle
(resistance to tumor metastases; role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT Antitumor agents
Muscle
(role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
IT **58-61-7, Adenosine**, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role for **A3 adenosine receptor agonists** in muscle resistance to tumor metastases)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bar-Yehuda, S; Clin Exp Metastasis 1999, V17, P531 HCAPLUS
(2) Birnbaum, M; Differentiation 1990, V45, P138 HCAPLUS
(3) Djaldetti, M; Clin Exp Metastasis 1996, V14, P189 HCAPLUS
(4) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(5) Fishman, P; Eur J Cancer 2000, V36, P1452 HCAPLUS
(6) Fishman, P; J Cellular Physiol 2000, V183, P393 HCAPLUS
(7) Husmann, I; Cytokine Growth Factor Rev 1996, V7, P249 HCAPLUS
(8) Ioachim, H; Hum Pathol 1983, V14, P924
(9) Jacobson, K; Drug Dev Res 1998, V45, P113 HCAPLUS
(10) Jacobson, K; Drug Dev Res 1998, V45, P113 HCAPLUS
(11) Jacobson, K; Drugs Future 1995, V20, P689
(12) Kurek, J; Muscle Nerve 1996, V19, P1291 MEDLINE
(13) Kurland, J; Cancer Res 1977, V37, P4534 HCAPLUS
(14) Lafyatis, R; Mol Cell Biol 1991, V7, P3795
(15) Lasser, A; Hum Pathol 1982, V13, P1045 MEDLINE
(16) Lee, A; Blood 1999, V93, P537 HCAPLUS
(17) Lee, E; Circ Res 1996, V78, P44 HCAPLUS
(18) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(19) Liu, G; Cardiovasc Res 1994, V28, P1057 HCAPLUS
(20) Merimsky, O; Tumori 1990, V76, P407 MEDLINE
(21) Pastan, I; Annu Rev Biochem 1975, V44, P491 HCAPLUS
(22) Pellegrini, A; Arch Surg 1979, V114, P550 MEDLINE
(23) Rosztoczy, I; Interferon Res 1989, V9, P509 HCAPLUS
(24) Sarma, D; J Surg Oncol 1985, V30, P103 MEDLINE
(25) Slatkin, D; Hum Pathol 1976, V7, P347 MEDLINE
(26) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(27) Takada, S; Biochem Mol Biol Int 1997, V43, P9 HCAPLUS
(28) von Lubitz, D; Eur Js Pharmacol 1994, V263, P59 HCAPLUS
(29) Zacks, S; J Histochem Cytochem 1973, V21, P703 HCAPLUS
(30) Zacks, S; J Histochem Cytochem 1973, V21, P895 HCAPLUS

L101 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:208100 HCAPLUS
DN 134:231860
TI Pharmaceutical compositions comprising an **adenosine receptor agonist** or antagonist for **cancer** treatment
IN **Fishman, Pnina**
PA **Can-Fite Technologies Ltd., Israel**
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM A61K031-00
ICS A61K031-7052; A61K031-7076; A61K031-708; A61K031-706; A61P039-00; A61P035-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001019360	A2	20010322	WO 2000-IL550	20000908
	WO 2001019360	A3	20020919		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI IL 1999-131864 A 19990910
IL 1999-133680 A 19991223
OS MARPAT 134:231860
AB **Adenosine receptor agonists** and antagonists, particularly an **agonist** which binds to the **A3 adenosine receptor**, are used for induction of prodn. or secretion of G-CSF within the body, prevention or treatment of toxic side effects of a drug or prevention or treatment of leukopenia, particularly drug-induced leukopenias, and inhibition of abnormal cell growth and proliferation. For example, a marked inhibition of **tumor** growth was obsd. in nude mice with established HCT-116 human colon **carcinoma** treated with 5-fluorouracil (5-FU, 30 mg/kg for 5 days), 2-chloro-N6-(2-iodobenzyl)-**adenosine**-5'-N-methyluronamide (**Cl-IB-MECA**, 6 mg/kg, every other day), and the combined therapy of **Cl-IB-MECA** and 5-FU. After 20 days a clear synergistic effect between **Cl-IB -MECA** and 5-FU in noting the **tumor** mass was seen.
ST **adenosine receptor agonist** antagonist oral **antitumor**; granulocyte colony stimulating factor purinoceptor **antitumor**
IT Purinoceptor **agonists**
(A1; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)
IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A1; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)
IT Purinoceptor **agonists**
Purinoceptor antagonists
(A2; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)
IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A2; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)
IT Purinoceptor **agonists**

(**A3**; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**A3**; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **Antitumor** agents
(colon **carcinoma**; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Intestine, **neoplasm**
(colon, **carcinoma**, inhibitors; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Bone marrow
Leukocyte
(differentiation and proliferation, induction of; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Leukocytopenia
(drug-induced; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Body weight
(loss, drug-induced; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **Antitumor** agents
(lymphoma; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **Antitumor** agents
(**melanoma**; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Toxicity
(myelotoxicity, prevention of; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **Antitumor** agents
Cell differentiation
Cell proliferation
(oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Drug delivery systems
(oral; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Drug interactions
(synergistic; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT Bone marrow
(toxicity, prevention of; oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT 51-21-8, Fluorouracil 23214-92-8, Doxorubicin
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **120442-40-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT **58-61-7, Adenosine**, biological studies 14114-46-6
37739-05-2, CCPA **41552-82-3**, N-Cyclopentyladenosine
102146-07-6, DPCPX **152918-14-4 152918-18-8, IB-MECA 152918-27-9, AB-MECA**
163042-96-4, Cl-IB-MECA
183721-15-5, MRS 1200 212329-37-8, MRS 1523
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

IT 143011-72-7, Granulocyte colony-stimulating factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oral compns. comprising **adenosine receptor agonist** or antagonist for prevention or treatment of toxic side effects and **cancer** treatment)

L101 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:878944 HCAPLUS
DN 134:157111
TI Differential effect of **adenosine** on tumor and normal cell growth: focus on the **A3 adenosine receptor**
AU Ohana, Gil; Bar-Yehuda, Sara; Barer, Faina; **Fishman, Pnina**
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Rabin Medical Center, Tel-Aviv University, Petach-Tikva, Israel
SO Journal of Cellular Physiology (2001), 186(1), 19-23
CODEN: JCLLAX; ISSN: 0021-9541
PB Wiley-Liss, Inc.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 47 refs. **Adenosine** is an ubiquitous nucleoside present in all body cells. It is released from metabolically active or stressed cells and subsequently acts as a regulatory mol. through binding to specific A1, A2A, A2B and **A3** cell surface **receptors**. The synthesis of **agonists** and antagonists to the **adenosine receptors** and their cloning enabled the exploration of their physiol. functions. As nearly all cells express specific **adenosine receptors, adenosine** serves as a physiol. regulator and acts as a cardioprotector, neuroprotector, chemoprotector, and as an immunomodulator. At the cellular level, activation of the **receptors** by **adenosine** initiates signal transduction mechanisms through G-protein assocd. **receptors. Adenosine**'s unique characteristic is to differentially modulate normal and transformed cell growth, depending upon its extracellular concn., the expression of **adenosine** cell surface **receptors**, and the physiol. state of the target cell. Stimulation of cell proliferation following incubation with

adenosine has been demonstrated in a variety of normal cells in the range of low micromolar concns., including mesangial and thymocyte cells, Swiss mouse 3T3 fibroblasts, and bone marrow cells. Induction of apoptosis in tumor or normal cells was shown at higher **adenosine** concns. (> 100 .mu.M) such as in leukemia HL-60, lymphoma U-937, A431 epidermoid cells, and GH3 tumor pituitary cell lines. It was further noted that the **A3 adenosine receptor** (**A3AR**) plays a key role in the inhibitory and stimulatory growth activities of **adenosine**. Modulation of the **A3AR** was found to affect cell growth either pos. or neg. depending on the concn. of the **agonist**, similar to the effect described for **adenosine**. At nanomolar concns., the **A3AR** **agonists** possess dual activity, i.e., anti-proliferative activity toward tumor cells and stimulatory effect on bone marrow cells. In vivo, these **agonists** exerted anti-cancer effects, and when given in combination with chemotherapy, they enhanced the chemotherapeutic index and acted as chemoprotective agents. Taken together, activation of the **A3AR**, by minute concns. of its natural ligand or synthetic **agonists**, may serve as a new approach for cancer therapy.

ST review **adenosine** antitumor **A3 receptor**

IT **Adenosine receptors**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**A3**; differential effect of **adenosine** on tumor and normal cell growth: focus on the **A3 adenosine receptor**)

IT Antitumor agents
(differential effect of **adenosine** on tumor and normal cell growth: focus on the **A3 adenosine receptor**)

IT **58-61-7**, **Adenosine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential effect of **adenosine** on tumor and normal cell growth: focus on the **A3 adenosine receptor**)

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

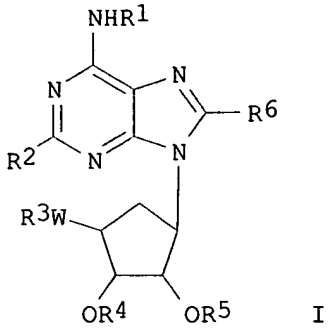
(1) Abbracchio, M; Drug Dev Res 1996, V38, P393
(2) Abbracchio, M; Drug Dev Res 1996, V39, P393 HCAPLUS
(3) Abbracchio, M; Mol Pharmacol 1995, V48, P1038 HCAPLUS
(4) Bajaj, S; Blood 1983, V62, P75 HCAPLUS
(5) Bouma, M; J Immunol 1994, V153, P4159 HCAPLUS
(6) Brambilla, R; Activation of the A3 adenosine receptor affects cell cycle progression and cell growth 2000, V361, P225 HCAPLUS
(7) Burnstock, G; Ciba Foundation Symposium 1996, V198, P1 HCAPLUS
(8) Burnstock, G; Drug Dev Res 1996, V39, P204 HCAPLUS
(9) Ceruti, S; Drug Dev Res 1996, V37, P177
(10) Chen, J; Drug Dev Res 2000, V50(1, special issue), P71
(11) Colquhoun, A; Cell Biochem Func 1997, V15(2), P135 HCAPLUS
(12) Dubey, K; Circulation 1997, V96(8), P2656
(13) Dubey, R; Hypertension 1996, V28, P7
(14) Dusseau, J; Respir Physiol 1988, V71, P33 HCAPLUS
(15) Farrow, S; Nature 1995, V374, P731 HCAPLUS
(16) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(17) Fishman, P; Eur J Cancer 2000, V36(11), P1452 HCAPLUS
(18) Fishman, P; J Cell Physiol 2000, V183, P393 HCAPLUS
(19) Freedholm, B; Pharmacol Rev 1994, V46, P143
(20) Gilbertsen, R; Agents Actions 1987, V22, P91 MEDLINE
(21) Gonzales, F; Proc Natl Acad Sci USA 1990, V87, P9717
(22) Kallassy, M; Mol Carcinog 1998, V21(1), P26 HCAPLUS

(23) Kizaki, H; J Immunol 1988, V141(5), P1652 HCAPLUS
(24) Kohno, Y; Biochem Biophys Res Commun 1996, V219, P904 HCAPLUS
(25) Lasely, R; Drug Dev Res 1996, V39, P314
(26) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(27) Multani, A; Int J Oncol 1999, V15(3), P423 HCAPLUS
(28) Phillis, J; Drug Dev Res 1993, V28, P390 HCAPLUS
(29) Pospisil, M; Blood 1995, V86, P3692 HCAPLUS
(30) Pospisil, M; Eur J Haematol 1998, V60, P172 HCAPLUS
(31) Pospisil, M; Radiat Res 1993, V134, P323 HCAPLUS
(32) Poulsen, S; Bioorg Med Chem 1998, V6, P619 HCAPLUS
(33) Poulsen, S; Bioorg Med Chem 1998, V9, P619
(34) Rozengurt, E; Exp Cell Res 1982, V139, P71 HCAPLUS
(35) Sandberg, G; Thymus 1981, V3, P63 HCAPLUS
(36) Soderback, U; Clin Sci 1991, V81, P691 MEDLINE
(37) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(38) Szondy, Z; Biochem J 1994, V364, P877
(39) Szondy, Z; Biochem J 1995, V311, P585 HCAPLUS
(40) Tanaka, Y; Exp Cell Res 1994, V213, P242 HCAPLUS
(41) Tey, H; Biochem Biophys Res Commun 1992, V187, P1481
(42) Vials, A; Br J Pharmacol 1993, V109, P424 HCAPLUS
(43) Von Lubitz, D; Ann NY Acad Sci 1995, V4, P163
(44) Von Lubitz, X; Drug Dev Res 1994, V33, P51
(45) Wakade, T; J Physiol 1995, V488, P123 HCAPLUS
(46) Xaus, J; J Immunol 1999, V163, P4140 HCAPLUS
(47) Yao, Y; Biochem Biophys Res Commun 1997, V232, P317 HCAPLUS

L101 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:475547 HCAPLUS
DN 133:84250
TI Use of adenosine agonists in cancer therapy for inducing proliferation of hematopoietic system cells
IN **Fishman, Pnina**; Cohn, Ilan
PA **Can-Fite Technologies Ltd., Israel**
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-70
ICS C07H019-16
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040251	A1	20000713	WO 2000-IL14	20000107
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1140116	A1	20011010	EP 2000-900112	20000107
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002534390	T2	20021015	JP 2000-592007	20000107
	US 2001031742	A1	20011018	US 2001-782259	20010214
	US 2002037871	A1	20020328	US 2001-871963	20010604
PRAI	IL 1999-127947	A	19990107		
	WO 2000-IL14	W	20000107		
	US 2001-700744	A2	20010109		

US 2001-782259 A2 20010214
OS MARPAT 133:84250
GI



I

AB Pharmaceutical compns. are provided for use in inducing proliferation of the hematopoietic system, in particular, of bone marrow cells, comprising a pharmaceutically acceptable carrier, excipient or diluent and, as an active ingredient, an effective amt. of an **adenosine** A1 **receptor agonist**. The pharmaceutical compn. of the invention may be used to induce proliferation of bone marrow cells, in a variety of clin. situations where such proliferation is therapeutically beneficial. The active ingredient within the pharmaceutical compn. of the invention may be I [R1 = lower alkyl, (un)substituted cycloalkyl, OH, hydroxyalkyl, etc.; R2 = H, halo, (un)substituted lower alkyl, etc.; R3-R5 = H, lower alkyl, lower alkenyl, etc.; R6 = H, halo, etc.; W = OCH2, NHCH2, SCH2, NHC(O)] or any other compd. or substance which specifically binds to and/or activates the A1 **adenosine receptor** and acts as an **agonist** to the **receptor**'s natural ligand.

ST adenosine agonist hematopoietic stimulation cancer therapy

IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A1; **adenosine agonists** in cancer therapy for inducing proliferation of hematopoietic system cells)

IT Antipsychotics
Antitumor agents
Bone marrow
Cell proliferation
Drug delivery systems
Immunomodulators
Leukocytopenia
Radiotherapy
Tranquilizers
(adenosine agonists in cancer therapy for inducing proliferation of hematopoietic system cells)

IT Agranulocytosis
(neutropenia; adenosine agonists in cancer therapy for inducing proliferation of hematopoietic system cells)

IT **58-61-7**, Adenosine, biological studies 14114-46-6, 3,7-Dimethyl-1-propargylxanthine 102146-07-6, 1,3-Dipropyl-8-cyclopentylxanthine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(adenosine agonists in cancer therapy for inducing proliferation of hematopoietic system cells)

IT **36396-99-3 37739-05-2**, 2-Chloro-N6-cyclopentyladenosine

41552-82-3, N6-Cyclopentyladenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine agonists in cancer therapy for inducing proliferation of hematopoietic system cells)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Glaxo Group Ltd; US 5998388 A HCAPLUS
(2) Glaxo Group Ltd; WO 9743300 A 1997 HCAPLUS
(3) Moos, W; JOURNAL OF MEDICINAL CHEMISTRY 1985, V28(10), P1383 HCAPLUS
(4) Tey, H; BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 1992, V187(3), P1486 HCAPLUS
(5) The United States Of America; US 5498605 A HCAPLUS
(6) The United States Of America; WO 9402497 A 1994 HCAPLUS
(7) Trivedi, B; US 4791103 A 1998 HCAPLUS
(8) University Of Florida; US 5998387 A HCAPLUS
(9) University Of Florida; WO 9724363 A 1997 HCAPLUS
(10) Williams, M; DRUG DEVELOPMENT RESEARCH 1993, V28(3), P438 HCAPLUS

L101 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:469347 HCAPLUS
DN 134:25148
TI **Adenosine** acts as an inhibitor of lymphoma cell growth. A major role for the **A3 adenosine receptor**
AU **Fishman, P.**; Bar-Yehuda, S.; Ohana, G.; Pathak, S.; Wasserman, L.; Barer, F.; Multani, A. S.
CS Felsenstein Medical Research Center, Laboratory of Clinical and Tumor Immunology, Rabin Medical Center, Tel-Aviv University, Petach-Tikva, Israel
SO European Journal of Cancer (2000), 36(11), 1452-1458
CODEN: EJCAEL; ISSN: 0959-8049
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB In this study, we demonstrated several mechanisms exploring the inhibitory effect of low-dose **adenosine** on lymphoma cell growth. **Adenosine**, a purine nucleoside present in plasma and other extracellular fluids, acts as a regulatory mol., by binding to G-protein-assocd. cell-surface **receptors**, A1, A2 and **A3** . Recently we showed that low-dose **adenosine** released by muscle cells, inhibits tumor cell growth and thus attributes to the rarity of muscle metastases. In the present work, a cytostatic effect of **adenosine** on the proliferation of the Nb2-11C rat lymphoma cell line was demonstrated. This effect was mediated through the induction of cell cycle arrest in the G0/G1 phase and by decreasing the telomeric signal in these cells. **Adenosine** was found to exert its antiproliferative effect mainly through binding to its **A3 receptor**. The cytostatic anticancer activity, mediated through the **A3 adenosine receptor**, turns it into a potential target for the development of anticancer therapies.
ST **adenosine** antitumor lymphoma **A3 adenosine receptor** telomere
IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; **adenosine** action as lymphoma inhibitor: **A3 adenosine receptor** role)
IT Telomeres (chromosome)
(**adenosine** action as lymphoma inhibitor: **A3 adenosine receptor** role)
IT Cell cycle
(arrest, G0/G1 phase; **adenosine** action as lymphoma inhibitor:

A3 adenosine receptor role)
IT Antitumor agents
(lymphoma; **adenosine** action as lymphoma inhibitor: **A3 adenosine receptor** role)
IT **58-61-7**, **Adenosine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adenosine** action as lymphoma inhibitor: **A3 adenosine receptor** role)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bajaj, S; Blood 1983, V62, P75 HCAPLUS
(2) Bowlin, T; Cell Mol Biol 1997, V43, P345 HCAPLUS
(3) Clarke, B; Int J Cardiol 1989, V23, P1 MEDLINE
(4) Collis, M; Pharmacol Ther 1989, V41, P143 HCAPLUS
(5) Colquhoun, A; Cell Biochem Funct 1997, V15, P135 HCAPLUS
(6) Dawicki, D; Am J Physiol 1997, V273(2), PL485 HCAPLUS
(7) Djaldetti, M; Clin Exp Metast 1996, V14, P189 HCAPLUS
(8) Elgler, A; Scand J Immunol 1997, V45, P132
(9) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(10) Gilbertsen, R; Agents Actions 1987, V22, P91 MEDLINE
(11) Hare, I; J Histochem Cytochem 1986, V34, P215
(12) Kallassy, M; Mol Carcinogen 1998, V21, P26 HCAPLUS
(13) Krishan, A; J Cell Biol 1975, V66, P188 MEDLINE
(14) Kurland, J; Cancer Res 1977, V37, P4534 HCAPLUS
(15) Lasely, R; Drug Dev Res 1996, V39, P314
(16) Lewis, M; Mol Cell Endocrinol 1997, V2, P137
(17) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(18) MacLaughlin, M; Cell Signal 1997, V9, P59 HCAPLUS
(19) Multani, A; Anticancer Res 1996, V16, P3435 MEDLINE
(20) Multani, A; Int J Oncol 1999, V15, P423 HCAPLUS
(21) Pathak, S; J Reprod Med 1976, V17, P25 MEDLINE
(22) Paul, P; J Lab Clin Med 1988, V112, P168 HCAPLUS
(23) Phillis, J; Drug Dev Res 1993, V28, P390 HCAPLUS
(24) Pines, M; J Cell Biochem 1988, V37, P119 HCAPLUS
(25) Poulsen, S; Bioorg Med Chem 1998, V6, P619 HCAPLUS
(26) Rayhel, E; J Cell Biochem 1990, V43, P327 HCAPLUS
(27) Sandberg, G; Int J Immunopharmacol 1983, V5, P259 HCAPLUS
(28) Seetulsingh-Goorah, S; Biochem Biophys Res Commun 1998, V18(250), P390
(29) Shimegi, S; Calcif Tissue Int 1998, V62, P418 HCAPLUS
(30) Skalhegg, B; J Cell Physiol 1998, V177, P85 HCAPLUS
(31) Soderback, U; Clin Sci 1991, V81, P691 MEDLINE
(32) Stambaugh, K; Am J Physiol 1997, V273, PH501 HCAPLUS
(33) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(34) Tanaka, Y; Exp Cell Res 1994, V213, P242 HCAPLUS
(35) Tey, H; Biochem Biophys Res Commun 1992, V30(187(3)), P1486
(36) Von Lubitz, D; Ann NY Acad Sci 1995, V4, P163
(37) Von Lubitz, D; Eur Pharmacol 1999, V19(367), P157
(38) Ward, A; Biochem Biophys Res Commun 1996, V224, P10 HCAPLUS
(39) Yao, Y; Biochem Biophys Res Commun 1997, V232, P317 HCAPLUS

L101 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:291051 HCAPLUS
DN 133:26585
TI **Adenosine** acts as a chemoprotective agent by stimulating G-CSF production: a role for A1 and **A3 adenosine receptors**
AU **Fishman, Pnina**; Bar-Yehuda, Sara; Farbstein, Tamar; Barer, Faina; Ohana, Gil
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Rabin Medical Center, Tel-Aviv University, Petach-Tikva, Israel

SO Journal of Cellular Physiology (2000), 183(3), 393-398
CODEN: JCLLAX; ISSN: 0021-9541
PB Wiley-Liss, Inc.
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 2

AB **Adenosine**, a ubiquitous nucleoside, is released into the extracellular environment from metabolically active or stressed cells. It binds to cells through specific A1, A2A, A2B, and **A3** G-protein-assocd. cell-surface **receptors**, thus acting as a signal-transduction mol. by regulating the levels of adenylyl cyclase and phospholipase C. In this study, we showed that **adenosine** stimulates the proliferation of murine bone marrow cells in vitro. Pharmacol. studies, using antagonists to the **adenosine** **receptors**, revealed that this activity was mediated through the binding of **adenosine** to its A1 and **A3** **receptors**. This result was further corroborated by showing that the two selective A1 and **A3** **receptor** **agonists**, N-cyclopentyladenosine (CPA) and 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl-.beta.-D-ribofuranuronamide (**IB-MECA**) resp., induced bone marrow cell proliferation in a manner similar to **adenosine**. **Adenosine**'s interaction with its A1 and **A3** **receptors** induced G-CSF prodn., which led to its stimulatory effect on bone marrow cells. These results were confirmed in vivo when we demonstrated that low-dose **adenosine** (0.25 mg/kg) acted as a chemoprotective agent. When administered after chemotherapy, it restored the no. of leukocytes and neutrophils to normal levels, compared with the decline in these parameters after chemotherapy alone. It is suggested that low-dose **adenosine**, already in clin. use, may also be applied as a chemoprotective agent.

ST adenosine chemoprotectant CSF receptor

IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A1; **adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3** **receptors** therein)

IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**A3**; **adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3** **receptors** therein)

IT Bone marrow
Cytoprotective agents
Hematopoiesis
Leukocyte
Neutrophil
Signal transduction, biological
(**adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3** **receptors** therein)

IT 50-18-0, Cyclophosphamide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3** **receptors** therein)

IT **41552-82-3**, N-Cyclopentyladenosine **152918-18-8**, **IB-MECA**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(**adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3 receptors** therein)

IT **58-61-7**, **Adenosine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3 receptors** therein)

IT 143011-72-7, Granulocyte-colony-stimulating factor
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**adenosine** acts as bone marrow chemoprotective agent by stimulating granulocyte-CSF prodn. and role for **adenosine** A1 and **A3 receptors** therein)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bastin, B; Cell Immunol 1990, V128, P385 HCAPLUS
(2) Belardinelli, L; Prog Cardiovasc Dis 1989, V32, P73 HCAPLUS
(3) Bouma, M; J Immunol 1994, V153, P4159 HCAPLUS
(4) Clarke, B; Int J Cardiol 1989, V23, P1 MEDLINE
(5) Collis, M; Pharmacol Ther 1989, V41, P143 HCAPLUS
(6) Cronstein, B; J Immunol 1992, V148, P2201 HCAPLUS
(7) Derigs, H; Exp Hematol 1994, V22, P924 HCAPLUS
(8) Djaldetti, M; Clin Exp Metastasis 1996, V14, P189 HCAPLUS
(9) Dubey, R; Circulation 1997, V96, P2656 HCAPLUS
(10) Epstein, J; Cancer Treat Rep 1984, V68, P1153 HCAPLUS
(11) Fishman, P; Cancer Res 1998, V58, P3181 HCAPLUS
(12) Gilbertsen, R; Agents Actions 1987, V22, P91 MEDLINE
(13) Ikebuchi, K; Blood 1988, V72, P2007 HCAPLUS
(14) Itoh, Y; Int J Hematol 1992, V55, P139 MEDLINE
(15) Jackson, R; Br J Cancer 1978, V37, P701 HCAPLUS
(16) Kitabayashi, A; Blood 1995, V86, P2220 HCAPLUS
(17) Krishan, A; J Cell Biol 1975, V66, P188 MEDLINE
(18) Kurland, J; Cancer Res 1977, V37, P4534 HCAPLUS
(19) Lee, A; Blood 1999, V93, P537 HCAPLUS
(20) Linden, J; FASEB J 1991, V5, P2668 HCAPLUS
(21) Nagao, S; Cell Immunol 1984, V89, P427 HCAPLUS
(22) Nilsson, J; Atherosclerosis 1984, V53, P77 HCAPLUS
(23) Parmely, M; J Immunol 1993, V151, P389 HCAPLUS
(24) Pastan, I; Annu Rev Biochem 1975, V44, P491 HCAPLUS
(25) Patil, R; Blood 1995, V85, P80 HCAPLUS
(26) Pospisil, M; Blood 1995, V86, P3692 HCAPLUS
(27) Pospisil, M; Eur J Haematol 1998, V60, P172 HCAPLUS
(28) Pospisil, M; Radiat Res 1993, V134, P323 HCAPLUS
(29) Robson, R; Kidney Int 1995, V48, P1767 HCAPLUS
(30) Soderback, U; Clin Sci 1991, V81, P691 MEDLINE
(31) Stiles, G; Clin Res 1990, V38, P10 MEDLINE
(32) Wagner, D; Circ Res 1998, V82, P47 HCAPLUS
(33) Ward, A; Biochem Biophys Res Commun 1996, V224, P10 HCAPLUS
(34) Wilson, N; Biochem Biophys Res Commun 1998, V244, P475 HCAPLUS

=> d all tot

L105 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **2001:879918** HCAPLUS
DN **136:161304**
TI Pharmacological and biochemical characterization of adenosine receptors in the human **malignant melanoma** A375 cell line
AU Merighi, Stefania; Varani, Katia; Gessi, Stefania; Cattabriga, Elena;

Iannotta, Valeria; Ulouglu, Canan; Leung, Edward; Borea, Pier Andrea
CS Department of Clinical and Experimental Medicine, Pharmacology Unit, Centro Nazionale Di Eccellenza Per Lo Sviluppo Di Metodologie Innovative Per Lo Studio Ed II Trattamento Delle Patologie Infiammatorie, University of Ferrara, Italy
SO British Journal of Pharmacology (2001), 134(6), 1215-1226
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 14
AB 1 The present work characterizes, from a pharmacol. and biochem. point of view, **adenosine receptors** in the human **malignant melanoma** A375 cell line. 2 **Adenosine receptors** were detected by RT-PCR expts. A1 **receptors** were characterized using [3H]-DPCPX binding with a KD of 1.9.+-.0.2 nM and Bmax of 23.+-.7 fmol mg-1 of protein. A2A **receptors** were studied with [3H]-SCH 58261 binding and revealed a KD of 5.1.+-.0.2 nM and a Bmax of 220.+-.7 fmol mg-1 of protein. **A3 receptors** were studied with the new **A3 adenosine receptor** antagonist [3H]-MRE 3008F20, the only **A3** selective radioligand currently available. Satn. expts. revealed a single high affinity binding site with KD of 3.3.+-.0.7 nM and Bmax of 291.+-.50 fmol mg-1 of protein. 3 The pharmacol. profile of radioligand binding on A375 cells was established using typical **adenosine** ligands which displayed a rank order of potency typical of the different **adenosine receptor** subtype. 4 Thermodn. data indicated that radioligand binding to **adenosine receptor** subtypes in A375 cells was entropy- and enthalpy-driven. 5 In functional assays the high affinity A2A **agonists** HE-NECA, CGS 21680 and A2A-A2B **agonist** NECA were able to increase cAMP accumulation in A375 cells whereas **A3 agonists Cl-IB -MECA, IB-MECA** and NECA were able to stimulate Ca2+ mobilization. 6 In conclusion, all these data indicate, for the first time, that **adenosine receptors** with a pharmacol. and biochem. profile typical of the A1, A2A, A2B and **A3 receptor** subtype are present on A375 **melanoma** cell line.
ST **melanoma** adenosine receptor biochem pharmacol
IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A1; pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)
IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2A; pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)
IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A2B; pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)
IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; pharmacol. and biochem. characterization of **adenosine receptors** in human **malignant melanoma** A375 cell line)
IT Enthalpy
Entropy
Melanoma
Pharmacology
Thermodynamics
(pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)

IT Adenosine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)
IT 60-92-4, CAMP 961-45-5, 8-Phenyltheophylline 7440-70-2, Calcium, biological studies 35788-27-3, 5'-(N-Methyl)carboxamidoadenosine 35873-49-5, 8-Cyclopentyltheophylline 35920-39-9, NECA 36396-99-3 38594-96-6, R-PIA 38594-97-7, S-PIA 41552-82-3, N6-Cyclopentyladenosine 102146-07-6, DPCPX 104615-18-1, CGS 15943 120225-54-9, CGS 21680 141018-30-6, HE-NECA **152918-18-8**, **IB-MECA** 160098-96-4, SCH 58261 **163042-96-4**, **Cl-IB-MECA** 252979-43-4, MRE 3008F20 361484-62-0, MRE 3048F20 361484-63-1, MRE 3055F20 361484-64-2, MRE 3062F20 396653-58-0, MRE 3046F20
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. and biochem. characterization of adenosine receptors in human **malignant melanoma** A375 cell line)
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abbracchio, M; Mol Pharmacol 1995, V48, P1038 HCAPLUS
(2) Ariza, M; J Biol Chem 1999, V274, P28505 HCAPLUS
(3) Arslan, G; Naunyn Schmiedebergs Arch Pharmacol 1999, V359, P28 HCAPLUS
(4) Baraldi, P; Bioorg Med Chem Lett 2000, V10, P209 HCAPLUS
(5) Baraldi, P; J Med Chem 1999, V42, P4473 HCAPLUS
(6) Baraldi, P; Trends Pharmacol Sci 2000, V21, P456 HCAPLUS
(7) Blackburn, M; J Biol Chem 1996, V271, P15203 HCAPLUS
(8) Blay, J; Cancer Res 1997, V57, P2602 HCAPLUS
(9) Borea, P; Life Sci 1996, V59, P1373 HCAPLUS
(10) Bradford, M; Anal Biochem 1976, V72, P248 HCAPLUS
(11) Brambilla, R; Naunyn Schmiedebergs Arch Pharmacol 2000, V361, P225 HCAPLUS
(12) Elenkov, I; Ann NY Acad Sci 2000, V917, P94 HCAPLUS
(13) Ethier, M; Am J Physiol 1993, V265, PH131 HCAPLUS
(14) Ethier, M; Am J Physiol 1997, V272, PH1470 HCAPLUS
(15) Feoktistov, I; Biochem Pharmacol 1998, V55, P627 HCAPLUS
(16) Fozard, J; Eur J Pharmacol 1996, V298, P293 HCAPLUS
(17) Fredholm, B; Biochem Pharmacol 2001, V61, P443 HCAPLUS
(18) Fredholm, B; Naunyn Schmiedebergs Arch Pharmacol 2000, V362, P364 HCAPLUS
(19) Fredholm, B; Physiol Rev 1994, V46, P143 HCAPLUS
(20) Gao, Z; Mol Pharmacol 2001, V59, P76 HCAPLUS
(21) Gessi, S; Br J Pharmacol 2000, V129, P2 HCAPLUS
(22) Gessi, S; Br J Pharmacol 2001, V134, P116 HCAPLUS
(23) Gilli, P; J Phys Chem 1994, V98, P1515 HCAPLUS
(24) Guieu, R; J Investig Med 2001, V49, P56 MEDLINE
(25) Jacobson, K; FEBS Lett 1993, V336, P57 HCAPLUS
(26) Jacobson, K; Trends Pharmacol Sci 1998, V19, P184 HCAPLUS
(27) Ji, X; Biochem Pharmacol 2001, V61, P657 HCAPLUS
(28) Klotz, K; Naunym Schmiedebergs Arch Pharmacol 2000, V362, P382 HCAPLUS
(29) Kohno, Y; Biochem Biophys Res Commun 1996, V219, P904 HCAPLUS
(30) Kohno, Y; Blood 1996, V88, P3569 HCAPLUS
(31) Liang, B; Proc Natl Acad Sci USA 1998, V95, P6995 HCAPLUS
(32) Marston, H; J Pharmacol Exp Ther 1998, V285, P1023 HCAPLUS
(33) Montesinos, M; J Exp Med 1997, V186, P1615 HCAPLUS
(34) Munson, P; Anal Biochem 1980, V107, P220 HCAPLUS
(35) Ohana, G; J Cell Physiol 2001, V186, P19 HCAPLUS
(36) Olah, M; Annu Rev Pharmacol Toxicol 1995, V35, P581 HCAPLUS
(37) Palmer, T; Neuropharmacology 1995, V34, P683 HCAPLUS
(38) Ralevic, V; Pharmacol Rev 1998, V50, P413 HCAPLUS
(39) Safran, N; Mol Cell Biochem 2001, V217, P143 HCAPLUS
(40) Schrier, S; Biochem Pharmacol 2001, V61, P417 HCAPLUS
(41) Tucker, A; Biochem J 2000, V352, P203 HCAPLUS
(42) Varani, K; Br J Pharmacol 1997, V122, P386 HCAPLUS
(43) Varani, K; Circulation 2000, V102, P285 HCAPLUS
(44) Varani, K; Mol Pharmacol 2000, V57, P968 HCAPLUS

(45) Walker, B; Am J Resp Cell Mol Biol 1997, V16, P531 HCAPLUS
(46) Walther, W; Biotechniques 1994, V17, P674 HCAPLUS
(47) Yao, Y; Biochem Biophys Res Comm 1997, V232, P317 HCAPLUS

L105 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **2001:688903** HCAPLUS
DN **135:339723**
TI Pharmacological characterization of adenosine receptors in PGT-.beta. mouse pineal gland tumour cells
AU Suh, Byung-Chang; Kim, Tae-Don; Lee, Jung-Uek; Seong, Je-Kyung; Kim, Kyong-Tai
CS Department of Life Science, Division of Molecular and Life Science, Pohang University of Science and Technology, Pohang, 790-784, S. Korea
SO British Journal of Pharmacology (2001), 134(1), 132-142
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB The **adenosine receptor** in mouse pinealocytes was identified and characterized using pharmacol. and physiol. approaches. Expression of the two **adenosine receptor** subtypes A2B and **A3** was detected in mouse pineal glands and PGT-.beta. cells by polymerase chain reaction and nucleotide sequencing. **Adenosine** and 5'-N-ethylcarboxamidoadenosine (NECA) evoked cAMP generation but the A2A-selective **agonist** 2-(4-(2-carboxyethyl)phenylethylamino) **adenosine**-5'-N-ethylcarboxamideadenosine (CGS 21680) and the A1-specific **agonists** R-N6-(2-phenylisopropyl)**adenosine** (R-PIA) and N6-cyclopentyladenosine (CPA) had little effect on intracellular cAMP levels. The A2B **receptor** selective antagonists alloxazine and enprofylline completely blocked NECA-mediated cAMP accumulation. Treatment of cells with the **A3**-selective **agonist** N6-(3-iodobenzyl)-5'-(N-methylcarbamoyl)**adenosine** (**IB-MECA**) inhibited the elevation of the cAMP level induced by NECA or isoproterenol in a concn.-dependent manner with maximal inhibition of 40-50%. These responses were blocked by the specific **A3 adenosine receptor** antagonist MRS 1191. Pretreatment of the cells with pertussis toxin attenuated the **IB -MECA**-induced responses, suggesting that this effect occurred via the pertussis toxin-sensitive inhibitory G proteins. **IB-MECA** also caused a concn.-dependent elevation in [Ca2+]i and IP3 content. Both the responses induced by **IB-MECA** were attenuated by treatment with U73122 or phorbol 12-myristate 13-acetate. These data suggest the presence of both A2B and **A3** **adenosine receptors** in mouse pineal **tumor** cells and that the A2B **receptor** is pos. coupled to adenylyl cyclase, whereas the **A3 receptor** is neg. coupled to adenylyl cyclase and also coupled to phospholipase C.
ST adenosine receptor characterization signaling pineal gland mouse
IT Adenosine receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(A2b; adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)
IT **Adenosine receptors**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**A3; adenosine receptors** pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)
IT G proteins (guanine nucleotide-binding proteins)

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gi (adenylate cyclase-inhibiting); adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT Mouse
Signal transduction, biological
Species differences
(adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT Phosphoinositides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT Pineal gland
(pinealocyte; adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT Adrenoceptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.2; .beta.2-adrenoceptor and adenosine receptor signaling interactions in PGT-.beta. mouse pineal gland **tumor** cells)

IT 58-61-7, Adenosine, biological studies 35920-39-9, 5'-N-Ethylcarboxamidoadenosine **152918-18-8**, **IB-MECA**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT 60-92-4, CAMP 9012-42-4, Adenylyl cyclase 63551-76-8, Phosphatidylinositol-specific phospholipase C 85166-31-0, Inositol trisphosphate 141436-78-4, Protein kinase C
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(intracellular; adenosine receptors pharmacol. characterization and function in PGT-.beta. mouse pineal gland **tumor** cells)

IT 7683-59-2, Isoproterenol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.2-adrenoceptor and adenosine receptor signaling interactions in PGT-.beta. mouse pineal gland **tumor** cells)

RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Auchampach, J; Mol Pharmacol 1997, V52, P846 HCAPLUS
(2) Babey, A; Neurosci Lett 1994, V176, P93 HCAPLUS
(3) Baraldi, P; Med Res Rev 2000, V20, P103 HCAPLUS
(4) Birnbaumer, L; Cell 1992, V71, P1069 HCAPLUS
(5) Brackett, L; Biochem Pharmacol 1994, V47, P801 HCAPLUS
(6) Brown, B; Biochem J 1971, V121, P561 HCAPLUS
(7) Challiss, R; Biochem J 1990, V265, P421 HCAPLUS
(8) Chomczynski, P; Biotechniques 1993, V15, P532 HCAPLUS
(9) Cunha, R; Neurochem Int 2001, V38, P107 HCAPLUS
(10) DI Virgilio, F; Biochem J 1988, V256, P959 HCAPLUS
(11) Ebadi, M; J Neural Transm Suppl 1986, V21, P125 HCAPLUS
(12) Falcon, J; Cell Tissue Res 1988, V251, P495 HCAPLUS
(13) Falcon, J; Eur J Pharmacol 1997, V337, P325 HCAPLUS
(14) Falcon, J; Pflugers Arch 1988, V413, P93 HCAPLUS
(15) Feinstein, P; Proc Natl Acad Sci U S A 1991, V88, P10173 HCAPLUS

(16) Ferreira, Z; Br J Pharmacol 1994, V112, P107 HCAPLUS
(17) Fredholm, B; Naunyn Schmiedebergs Arch Pharmacol 2000, V362, P364 HCAPLUS
(18) Gallo-Rodriguez, C; J Med Chem 1994, V37, P636 HCAPLUS
(19) Gharib, A; Eur J Pharmacol 1992, V225, P359 MEDLINE
(20) Goto, M; J Pineal Res 1989, V7, P195 HCAPLUS
(21) Goto, M; Mol Brain Res 1994, V21, P349 HCAPLUS
(22) Grynkiewicz, G; J Biol Chem 1985, V260, P3440 HCAPLUS
(23) Haas, H; Naunyn Schmiedebergs Arch Pharmacol 2000, V362, P375 HCAPLUS
(24) Jacobson, K; FEBS Lett 1993, V336, P57 HCAPLUS
(25) Jacobson, K; J Med Chem 1995, V38, P1720 HCAPLUS
(26) Jacobson, K; Neuropharmacology 1997, V36, P1157 HCAPLUS
(27) Klotz, K; Naunyn Schmiedebergs Arch Pharmacol 1998, V357, P1 HCAPLUS
(28) Klotz, K; Naunyn Schmiedebergs Arch Pharmacol 2000, V362, P382 HCAPLUS
(29) Linden, J; Mol Pharmacol 1993, V44, P524 HCAPLUS
(30) Mortani, B; Eur J Pharmacol 2000, V401, P59
(31) Nicholls, J; J Pineal Res 1997, V23, P164 HCAPLUS
(32) Nikodijevic, O; Endocrinology 1989, V125, P2150 HCAPLUS
(33) Olah, M; Mol Pharmacol 1994, V45, P978 HCAPLUS
(34) Palmer, T; Mol Pharmacol 1997, V52, P632 HCAPLUS
(35) Palmer, T; Neuropharmacology 1995, V34, P683 HCAPLUS
(36) Park, D; J Biol Chem 1993, V268, P4573 HCAPLUS
(37) Park, J; Endocrinology 1997, V138, P617 HCAPLUS
(38) Ralevic, V; Pharmacol Rev 1998, V50, P413 HCAPLUS
(39) Ramkumar, V; Biochim Biophys Acta 1993, V1179, P89 HCAPLUS
(40) Ramkumar, V; Mol Pharmacol 1991, V40, P639 HCAPLUS
(41) Roseboom, P; Mol Brain Res 1998, V63, P189 HCAPLUS
(42) Sakamoto, K; Neurosci Lett 1998, V250, P181 HCAPLUS
(43) Sanger, F; Proc Natl Acad Sci U S A 1992, V74, P5463
(44) Shearman, L; Brain Res 1997, V745, P10 HCAPLUS
(45) Simon, M; Science 1991, V252, P802 HCAPLUS
(46) Son, J; Mol Brain Res 1996, V37, P32 HCAPLUS
(47) Sternweiss, P; Curr Opin Cell Biol 1994, V6, P198
(48) Suh, B; Br J Pharmacol 1999, V126, P399 HCAPLUS
(49) Suh, B; J Neurochem 1995, V64, P1071 HCAPLUS
(50) Suh, B; J Neurochem 1997, V68, P1622 HCAPLUS
(51) Tang, W; Science 1991, V254, P1500 HCAPLUS
(52) Trincavelli, M; J Neurochem 2000, V75, P1493 HCAPLUS
(53) van Muijlwijk-Koezen, J; J Med Chem 2000, V43, P2227 HCAPLUS

L105 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **2001:549711** HCAPLUS
DN **136:273473**
TI The **A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins
AU Abbracchio, Maria P.; Camurri, Alessandra; Ceruti, Stefania; Cattabeni, Flaminio; Falzano, Loredana; Giammarioli, Anna Maria; Jacobson, Kenneth A.; Trincavelli, Letizia; Martini, Claudia; Malorni, Walter; Fiorentini, Carla
CS Department of Pharmacological Sciences, University of Milan, Milan, 20133, Italy
SO Annals of the New York Academy of Sciences (2001), 939(Neuroprotective Agents), 63-73
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB In previous studies, we have demonstrated that exposure of astroglial cells to **A3 adenosine receptor** **agonists** results in dual actions on cell survival, with "trophic" and antiapoptotic effects at nanomolar concns. and induction of cell death at micromolar **agonist** concns. The protective actions of

A3 agonists have been assocd. with a reinforcement of the actin cytoskeleton, which likely results in increased resistance of cells to **cytotoxic** stimuli. The mol. mechanisms at the basis of this effect and the signaling pathway(s) linking the **A3 receptor** to the actin cytoskeleton have never been elucidated. Based on previous literature data suggesting that the actin cytoskeleton is controlled by small GTP-binding proteins of the Rho family, in the study reported here we investigated the involvement of these proteins in the effects induced by **A3 agonists** on human **astrocytoma** ADF cells. The presence of the **A3 adenosine receptor** in these cells has been confirmed by immunoblotting anal. As expected, exposure of human **astrocytoma** ADF cells to nanomolar concns. of the selective **A3 agonist 2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide** (CI-**IB-MECA**) resulted in formation of thick actin pos. stress fibers. Preexposure of cells to the C3B toxin that inactivates Rho-proteins completely prevented the actin changes induced by CI-**IB-MECA**. Exposure to the **A3 agonist** also resulted in significant redn. of Rho-GDI, an inhibitory protein known to maintain Rho proteins in their inactive state, suggesting a potentiation of Rho-mediated effects. This effect was fully counteracted by the concomitant exposure to the selective **A3 receptor** antagonist MRS1191. These results suggest that the reinforcement of the actin cytoskeleton induced by **A3 receptor agonists** is mediated by an interference with the activation/inactivation cycle of Rho proteins, which may, therefore, represent a biol. target for the identification of novel neuroprotective strategies.

ST **astrocytoma** cytoskeleton rearrangement **A3 adenosine receptor** rho protein

IT Purinoceptor **agonists**
(**A3**; **A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT Human
Signal transduction, biological
(**A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT Actins
Rho protein (G protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT **Adenosine receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**A3**; **A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT Astrocyte
(**astrocytoma**; **A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT Cytoprotective agents
(neuroprotectants; **A3 adenosine receptor** induces cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

IT **163042-96-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**A3 adenosine receptor** induces

cytoskeleton rearrangement in human **astrocytoma** cells via a specific action on rho proteins)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abbracchio, M; Ann NY Acad Sci 1999, V890, P79 HCAPLUS
(2) Abbracchio, M; Biochem Biophys Res Commun 1997, V241, P297 HCAPLUS
(3) Abbracchio, M; Drug Dev Res 1998, V45, P379 HCAPLUS
(4) Abbracchio, M; Mol Pharmacol 1995, V48, P1038 HCAPLUS
(5) Aullo, P; EMBO J 1993, V12, P921 HCAPLUS
(6) Barbieri, D; Neurochem Int 1997, V32, P493
(7) Bishop, A; Biochem J 2000, V348, P241 HCAPLUS
(8) Brambilla, R; N-S Arch Pharmacol 2000, V361, P224
(9) Fiorentini, C; Infect Immun 1998, V66, P2660 HCAPLUS
(10) Fiorentini, C; J Biol Chem 1997, V272, P19532 HCAPLUS
(11) Fredholm, B; Pharm Rev 1994, V46, P143 HCAPLUS
(12) Gallo-Rodriguez, C; J Med Chem 1994, V37, P636 HCAPLUS
(13) Hall, A; Science 1998, V279, P509 HCAPLUS
(14) Hannon, J; Br J Pharmacol 1995, V115, P945 HCAPLUS
(15) Hirao, M; J Cell Biol 1996, V135, P37 HCAPLUS
(16) Jacobson, K; Apoptosis 1999, V4, P197 HCAPLUS
(17) Jacobson, K; FEBS Lett 1993, V336, P57 HCAPLUS
(18) Jacobson, K; Neuropharmacol 1997, V36, P1157 HCAPLUS
(19) Kim, H; J Med Chem 1994, V37, P3614 HCAPLUS
(20) Kim, Y; J Med Chem 1996, V39, P4142 HCAPLUS
(21) Kitagawa, K; Brain Res 1990, V528, P21 MEDLINE
(22) Kohno, Y; Biochem Biophys Res Commun 1996, V219, P904 HCAPLUS
(23) Liang, B; Proc Natl Acad Sci USA 1998, V95, P6995 HCAPLUS
(24) Linden, J; Trends Pharmacol Sci 1994, V15, P298 HCAPLUS
(25) Malorni, W; Cell Biol Toxicol 1994, V10, P207 HCAPLUS
(26) Seasholtz, T; Mol Pharmacol 1999, V55, P949 HCAPLUS
(27) Sei, Y; Drug Dev Res 1997, V40, P267 HCAPLUS
(28) Stambaugh, C; Am J Physiol 1997, V273, PH501
(29) Von Lubitz, D; Ann NY Acad Sci 1999, V890, P93 HCAPLUS
(30) von Lubitz, D; Eur J Pharmacol 1994, V263, P59 HCAPLUS
(31) Yao, Y; Biochem Biophys Res Commun 1997, V232, P317 HCAPLUS

L105 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:13439** HCAPLUS
DN **128:136727**
TI The **A3 adenosine receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL: studies in human astroglioma cells
AU Abbracchio, Maria P.; Rainaldi, Gabriella; Giammarioli, Anna Maria; Ceruti, Stefania; Brambilla, Roberta; Cattabeni, Flaminio; Barbieri, Daniela; Franceschi, Claudio; Jacobson, Kenneth A.; Malorni, Walter
CS Institute of Pharmacological Sciences, Milan, Italy
SO Biochemical and Biophysical Research Communications (1997), 241(2), 297-304
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB The pathophysiol. role of the **adenosine A3 receptor** in the central nervous system is largely unknown. The authors have investigated the effects of the selective **A3 receptor agonist** 2-chloro-N6-(3-iodobenzyl)-**adenosine**, CI-**IB-MECA**, in cells of the astroglial lineage (human **astrocytoma** ADF cells). A marked reorganization of the cytoskeleton, with appearance of stress fibers and numerous cell protrusions, was found following exposure of cells to low (nM) concns. of CI-**IB-MECA**. These "trophic" effects were accompanied by induction of the expression of Rho, a small

GTP-binding protein, which was virtually absent in control cells, and by changes of the intracellular distribution of the antiapoptotic protein Bcl-xL, that, in **agonist**-exposed cells, became specifically assocd. to cell protrusions. This is the first demonstration that the intracellular organization of Bcl-xL can be modulated by the activation of a G-protein-coupled membrane **receptor**, such as the **A3 adenosine receptor**. Moreover, modulation of the astrocytic cytoskeleton by **adenosine** may have intriguing implications in both nervous system development and in the response of the brain to trauma and ischemia.

ST adenosine receptor astrocyte cytoskeleton antiapoptotic protein

IT **Adenosine receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**A3; adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bcl-x, Bcl-xL; **adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Actins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(F-; **adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Apoptosis
Astrocyte
Brain
Cell membrane
Cell morphology
Cytoskeleton
Signal transduction, biological
(**adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT G protein-coupled **receptors**
Rho protein (G protein)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Spreading
(biol.; **adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Biological transport
(intracellular; **adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT Organelle
(stress fiber; **adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-xL in human astroglioma cells)

IT 58-61-7, **Adenosine**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**adenosine A3 receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of

Bcl-xL in human astroglioma cells)

L105 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **1996:274498** HCAPLUS
DN **125:75515**
TI Induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists**.
[Erratum to document cited in CA124:250079]
AU Kohno, Yutaka; Sei, Yoshitatsu; Koshiba, Masahiro; Kim, Hea O.; Jacobson, Kenneth A.
CS Molecular Recognition Section, National Institutes Health, Bethesda, MD, 20892, USA
SO Biochemical and Biophysical Research Communications (1996), 221(3), 849
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The errors were not reflected in the abstr. or the index entries.
ST erratum **antitumor** leukemia apoptosis adenosine A3; **antitumor** leukemia apoptosis adenosine A3 erratum; leukemia apoptosis adenosine A3 agonist erratum
IT Apoptosis
(induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists** (Erratum))
IT **Neoplasm** inhibitors
(leukemia, induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists** (Erratum))
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**purinergic A3, agonists**; induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists** (Erratum))
IT 58-61-7D, **Adenosine, Adenosine**, analogs 35920-39-9, Neca 41552-82-3, N6-Cyclopentyladenosine 96865-92-8, Xac 120225-54-9, Cgs21680 **152918-18-8 163042-96-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists** (Erratum))

L105 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **1996:252943** HCAPLUS
DN **124:308239**
TI Inhibition of TNF-.alpha. expression by **adenosine**. Role of **A3 adenosine receptors**
AU Sajjadi, Fereydoun G.; Takabayashi, Ken; Foster, Alan C.; Domingo, Ron C.; Firestein, Gary S.
CS Gensia, Inc., San Diego, CA, 92121, USA
SO Journal of Immunology (1996), 156(9), 3435-42
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB **Adenosine agonists** inhibit TNF-.alpha. prodn. in macrophage and monocytes, but the mechanism is unknown. Therefore, we studied the human macrophage cell line U937 to det. the **adenosine**

receptor subtypes responsible and the intracellular signaling mechanisms involved. The A1/**A3 agonist** N6-(4-amino-3-iodobenzyl)**adenosine** (I-ABA) decreased LPS-stimulated TNF-.alpha. protein prodn. by 79%. The mechanism was pretranslational, as **adenosine receptor** stimulation caused a marked decrease in TNF-.alpha. mRNA. IL-1.beta., IL-6, and IL-8 mRNA were not changed by **adenosine agonists**. The rank order of **agonists** as TNF-.alpha. inhibitors suggested that the **A3 receptor** might be involved (N6-(3-iodobenzyl)-9-[5-(methylcarbamoyl)-.beta.-D-ribofuranosyl]**adenosine** > 2-chloroadenosine .gtoreq. I-ABA > N6-benzyl-5'-N-ethylcarboxamidoadenosine > NECA > CGS21680 > N6-cyclohexyladenosine), and this was supported by the fact that a mixed A1/**A3** antagonist (xanthine amine congener) reversed the effect, whereas A1-specific (1,3-dipropyl-8-cyclopentylxanthine) and A2-specific (3,7-dimethyl-1-propargylxanthine) antagonists did not. **Receptor** signaling did not involve cAMP or protein kinase A, nor did it alter the activation and binding characteristics of the transcription factor NF-.kappa.B. However, the compn. of the AP-1 transcription complex was altered by I-ABA. These data suggest that stimulation of the **A3 adenosine receptor** can alter the cytokine milieu by decreasing TNF-.alpha.. **Adenosine agonists** or **adenosine** regulating agents have potential therapeutic uses in acute and chronic inflammatory diseases.

ST TNFalpha **adenosine A3 receptor**

IT Macrophage
(**adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(AP-1 (activator protein 1), **adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

IT **Receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**purinergic A3**, **adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tumor** necrosis factor-.alpha., **adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

IT 58-61-7, **Adenosine**, biological studies 146-77-0, 2-Chloroadenosine 35920-39-9, NECA 36396-99-3 98866-49-0 120225-54-9, CGS21680
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

IT **152918-18-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(re; **adenosine** inhibition of TNF-.alpha. expression by human macrophage cell line mediation by **A3 receptors**)

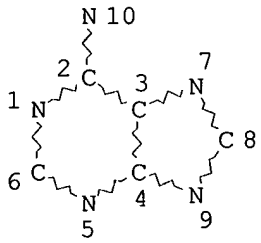
L105 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **1996:162478** HCAPLUS
DN **124:250079**
TI Induction of apoptosis in HL-60 human promyelocytic leukemia cells by

adenosine A3 receptor agonists
AU Kohno, Yutaka; Sei, Yoshitatsu; Koshiba, Masahiro; Kim, Hea O.; Jacobson, Kenneth A.
CS Molecular Recognition Section, National Institutes Health, Bethesda, MD, 20892, USA
SO Biochemical and Biophysical Research Communications (1996), 219(3), 904-10
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The effects of **adenosine** (ADO) analogs on cells of the human promyelocytic HL-60 line were examd. ADO **A3 receptor agonists**, N6-(3-iodobenzyl)**adenosine**-5'-N-methylcarboxamide (**IB-MECA**, 30-60 .mu.M) and **2-chloro-N6-(3-iodobenzyl) adenosine-5'-N-methyluronamide** (CI-**IB-MECA**, 10-30 .mu.M) induced apoptotic cell death. In contrast, neither an A1/A2 antagonist (XAC) nor other selective ADO **receptor agonists** (CPA, NECA and CGS21680) induced apoptosis at concns. of .ltoreq.30 .mu.M. Both **IB-MECA** and CI-**IB-MECA** significantly induced Ca2+ release from intracellular Ca2+ pools followed by Ca2+ pools followed by Ca2+ influx, suggesting the presence of phospholipase C-coupled ADO **A3 receptors** on HL-60 cells. This was further supported by the presence of mRNA of ADO **A3 receptor** in the cells. These results suggest that activation of ADO **A3 receptors** is responsible for the ADO-induced apoptosis in HL-60 cells and could be of potential therapeutic value in the treatment of leukemia.
ST **antitumor** leukemia apoptosis adenosine A3 agonist
IT Apoptosis
(induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists**)
IT **Neoplasm** inhibitors
(leukemia, induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists**)
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**purinergic A3, agonists**; induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists**)
IT 58-61-7D, **Adenosine**, analogs 35920-39-9, Neca 41552-82-3, N6-Cyclopentyladenosine 96865-92-8, Xac 120225-54-9, Cgs21680 **152918-18-8 163042-96-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A3 receptor agonists**)

L105 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2002 ACS
AN **1995:706870** HCAPLUS
DN **123:102310**
TI Therapeutic aspects of adenosine in relation to its anti-TNF properties.
AU Giroud, Jean-Paul; Lian Chen, Yan; Le Vraux, Valerie; Chauvelot-Moachon, Laurence
CS Departement de Pharmacologie, Hopital Cochin, Paris, 75679/14, Fr.
SO Bulletin de l'Academie Nationale de Medecine (Paris) (1995), 179(1), 79-101
CODEN: BANMAC; ISSN: 0001-4079
PB Academie Nationale de Medecine

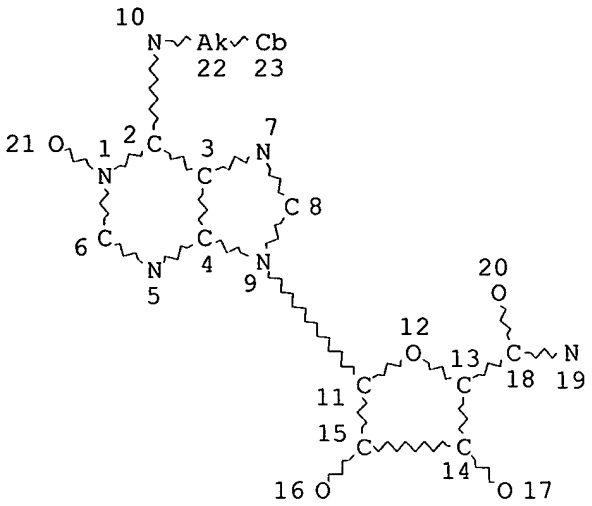
DT Journal
LA French
CC 1-7 (Pharmacology)
AB Expts. tested the hypothesis that the antiinflammatory properties of **adenosine** occur via a down-regulation of **tumor** necrosis factor (TNF). **Adenosine receptor agonists** (ARA) and agents potentiating endogenous **adenosine** (APA) were evaluated for their effects on TNF prodn. by endotoxin-stimulated human monocytes. Addnl., one of the most potent **agonists**, (R)-phenylisopropyladenosine (R-PIA), was tested in 2 exptl. models of acute-phase response: endotoxin shock and carrageenan-induced plantar edema. Several ARA and APA inhibited monocyte TNF prodn. in a concn.-dependent manner. R-PIA and other ARA were active at micromolar concns. This property is pharmacol. relevant, since rats receiving a LD of endotoxin were protected by R-PIA, and the endotoxin-induced increase in serum TNF levels was abolished by pretreatment with R-PIA. Inhibitory effects on serum TNF prodn. were obtained with similar concns. of dexamethasone and 100-fold higher concns. of pentoxifylline. R-PIA was also active on carrageenan-induced edema. The antiedema properties of R-PIA were assocd. with a marked redn. of locally produced TNF and were also obsd. after the administration of dexamethasone, pentoxifylline and a neutralizing anti-TNF antibody. The results indicate that **adenosine** is a potent inhibitor of TNF prodn. induced by different stimuli. This property could lead to therapeutic applications in inflammatory diseases and other conditions in which TNF is known to play a pathogenic or aggravating role.
ST adenosine antiinflammatory **tumor** necrosis factor; TNF prodn adenosine antiinflammatory
IT Inflammation inhibitors
(adenosine as)
IT Monocyte
(**tumor** necrosis factor prodn. by monocyte response to adenosine and its agonists)
IT Neurotransmitter agonists
(purinergic, **tumor** necrosis factor prodn. by monocyte response to adenosine and its agonists)
IT Lymphokines and Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tumor** necrosis factor-.alpha., pharmacol. effects of adenosine and adenosine agonists in relation to inhibition of **tumor** necrosis factor prodn.)
IT 50-02-2, Dexamethasone 6493-05-6, Pentoxifylline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. effects of adenosine and adenosine agonists in comparison with)
IT 58-61-7, Adenosine, biological studies 146-77-0, 2-Chloroadenosine 35920-39-9, 5'-N-Ethylcarboxamidoadenosine 36396-99-3 38594-96-6, (-)-Phenylisopropyladenosine 53296-10-9, CV 1808 **89705-21-5** 120225-54-9, CGS 21680
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. effects of adenosine and adenosine agonists in relation to inhibition of **tumor** necrosis factor prodn.)

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 16:08:40 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 OCT 2002  HIGHEST RN 463296-69-7
DICTIONARY FILE UPDATES:  20 OCT 2002  HIGHEST RN 463296-69-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que
L8       181680 SEA FILE=REGISTRY ABB=ON  PLU=ON  333.446/RID
L9              STR
```




```
NODE ATTRIBUTES:
NSPEC   IS RC     AT  10
CONNECT IS M1  RC AT   1
CONNECT IS M1  RC AT   6
CONNECT IS M1  RC AT   9
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   1
NUMBER OF NODES IS  10

STEREO ATTRIBUTES: NONE
L11       56975 SEA FILE=REGISTRY SUB=L8 CSS FUL L9
L12             STR
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov



NODE ATTRIBUTES:
NSPEC IS RC AT 19
CONNECT IS M1 RC AT 6
CONNECT IS M1 RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE
L13 0 SEA FILE=REGISTRY SUB=L11 CSS FUL L12

100.0% PROCESSED 4 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

=> fil reg
FILE 'REGISTRY' ENTERED AT 16:47:55 ON 21 OCT 2002

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 20 OCT 2002 HIGHEST RN 463296-69-7
DICTIONARY FILE UPDATES: 20 OCT 2002 HIGHEST RN 463296-69-7

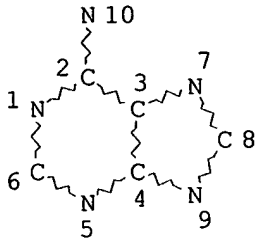
TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

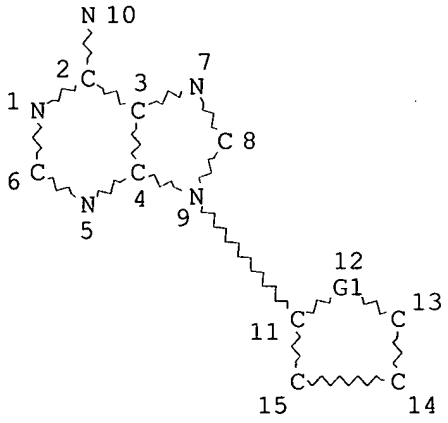
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

```
=> d sta que l39
L8       181680 SEA FILE=REGISTRY ABB=ON  PLU=ON  333.446/RID
L9              STR
```

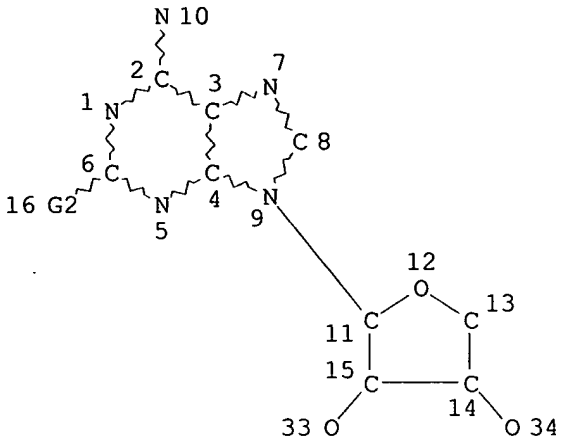



```
NODE ATTRIBUTES:
NSPEC   IS RC     AT  10
CONNECT IS M1  RC AT   1
CONNECT IS M1  RC AT   6
CONNECT IS M1  RC AT   9
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   1
NUMBER OF NODES IS  10

STEREO ATTRIBUTES: NONE
L11      56975 SEA FILE=REGISTRY SUB=L8 CSS FUL L9
L18             STR
```




```
VAR G1=O/S/C
NODE ATTRIBUTES:
NSPEC   IS RC     AT  10
CONNECT IS M1  RC AT   6
CONNECT IS M1  RC AT  10
CONNECT IS M1  RC AT  13
CONNECT IS M1  RC AT  14
CONNECT IS M1  RC AT  15
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   9
NUMBER OF NODES IS  15

STEREO ATTRIBUTES: NONE
```

L20 47535 SEA FILE=REGISTRY SUB=L11 CSS FUL L18
L21 STR

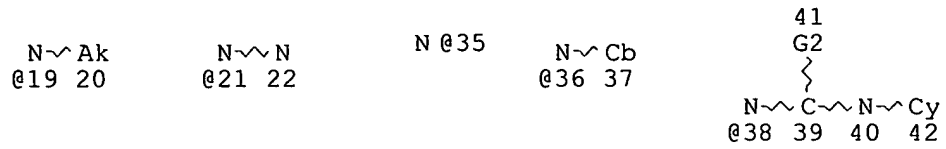


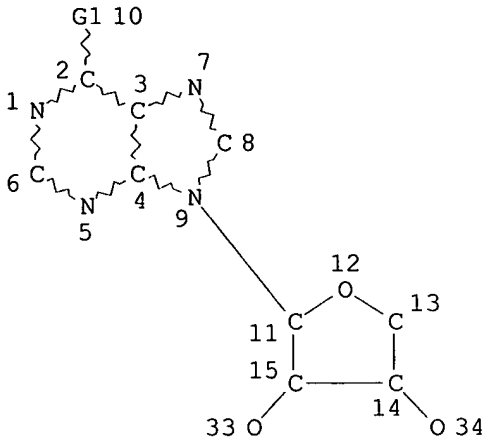
O~Ak @17 18
N~Ak @19 20
N~N @21 22
Ak~O~Ak @23 24 25
O~Ak~S @26 27 28
S~Ak @29 30
S~Hy @31 32

VAR G2=H/X/AK/S/N/17/19/21/23/26/29/31
NODE ATTRIBUTES:
NSPEC IS RC AT 10
CONNECT IS M1 RC AT 10
CONNECT IS M1 RC AT 13
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 32
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E5 C E1 N AT 32

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 34

STEREO ATTRIBUTES: NONE
L23 10896 SEA FILE=REGISTRY SUB=L20 CSS FUL L21
L24 STR

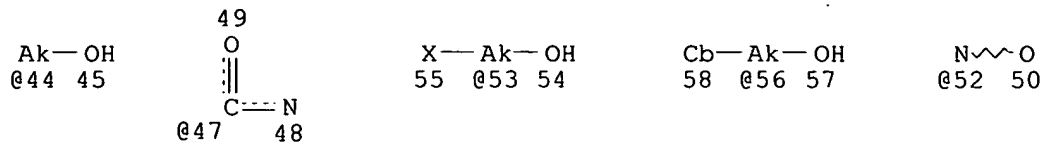


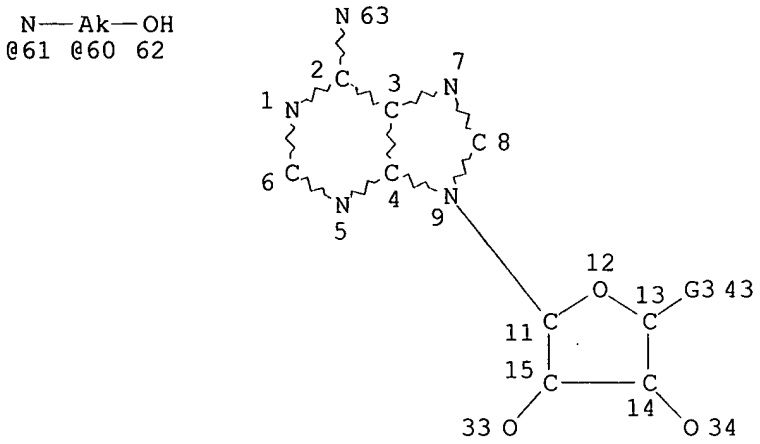


VAR G1=N/35/19/38/21/36
VAR G2=O/S
NODE ATTRIBUTES:
NSPEC IS R AT 35
CONNECT IS M1 RC AT 6
CONNECT IS M1 RC AT 13
CONNECT IS M1 RC AT 20
CONNECT IS M1 RC AT 22
CONNECT IS M1 RC AT 35
CONNECT IS M1 RC AT 37
CONNECT IS M1 RC AT 42
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 9
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
L26 10891 SEA FILE=REGISTRY SUB=L23 CSS FUL L24
L27 STR






```
VAR G3=H/AK/47/44/52/53/60/56/61
NODE ATTRIBUTES:
NSPEC   IS RC     AT  48
NSPEC   IS RC     AT  63
CONNECT IS M1  RC AT   6
CONNECT IS M1  RC AT  48
CONNECT IS M1  RC AT  53
CONNECT IS M1  RC AT  61
CONNECT IS M1  RC AT  63
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   9
NUMBER OF NODES IS  34

STEREO ATTRIBUTES: NONE
L29          843 SEA FILE=REGISTRY SUB=L26 CSS FUL L27
L30          744 SEA FILE=REGISTRY ABB=ON  PLU=ON  L29 NOT (PMS OR MNS OR
                 IDS)/CI
L31          640 SEA FILE=REGISTRY ABB=ON  PLU=ON  L30 NOT COMPD
L32          582 SEA FILE=REGISTRY ABB=ON  PLU=ON  L31 NOT SQL/FA
L33           75 SEA FILE=REGISTRY ABB=ON  PLU=ON  L32 AND NC>=2
L34           42 SEA FILE=REGISTRY ABB=ON  PLU=ON  L33 NOT MXS/CI
L35           27 SEA FILE=REGISTRY ABB=ON  PLU=ON  L34 NOT 58-61-7/CRN
L36          507 SEA FILE=REGISTRY ABB=ON  PLU=ON  L32 NOT L33
L37          506 SEA FILE=REGISTRY ABB=ON  PLU=ON  L36 NOT 58-61-7
L38          417 SEA FILE=REGISTRY ABB=ON  PLU=ON  L37 NOT (11C# OR 13C# OR
                 14C# OR C11# OR C13# OR C14# OR (D OR T)/ELS OR LABELED OR 15N
                 OR 18O OR 17O)
L39          444 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L35 OR L38)


=> d his 139-

     (FILE 'REGISTRY' ENTERED AT 16:08:40 ON 21 OCT 2002)
L39          444 S L35,L38
```

```
                SAV L39 YOUNG832F/A

     FILE 'HCAPLUS' ENTERED AT 16:42:11 ON 21 OCT 2002
L40         4425 S L39
L41         4294 S L40 AND PY<=2001
L42         4079 S L41 AND PY<=2000
L43            6 S L42 AND KILLER
L44            6 S L42 AND (NATURAL KILLER OR KILLER CELL OR NK)
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 16:44:13 ON 21 OCT 2002
L45            3 S E1-E3

     FILE 'HCAPLUS' ENTERED AT 16:44:30 ON 21 OCT 2002
                 E LYMPHOCYTE/CT
                 E E3+ALL
L46       143935 S E19,E18+NT
L47         4509 S E72+NT
L48           80 S L42 AND L46,L47
L49          754 S L42 AND (?NEOPLAS? OR ?TUMOR? OR ?MALIGN? OR ?METAST? OR ?CYO
L50          298 S L49 AND NEOPLAS?/CW
L51            2 S L50 AND L44
L52            6 S L44 AND L45,L47
L53            6 S L51,L52

     FILE 'REGISTRY' ENTERED AT 16:47:55 ON 21 OCT 2002

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:48:11 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 21 Oct 2002  VOL 137 ISS 17
FILE LAST UPDATED: 20 Oct 2002  (20021020/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d all hitstr tot l53

L53  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2002 ACS
AN   2001:128431  HCAPLUS
DN   135:136372
TI   Increased cytotoxicity against B-chronic lymphocytic leukemia by cellular
     manipulations: potentials for therapeutic use
AU   Vu, U. Eileen; Pavletic, Z. Steven; Wang, Xiaojun; Joshi, Shantaram S.
```

CS Departments of Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha, NE, 68198-6395, USA
SO Leukemia & Lymphoma (2000), 39(5/6), 573-582
CODEN: LELYEA; ISSN: 1042-8194
PB Harwood Academic Publishers
DT Journal
LA English
CC 15-10 (Immunochemistry)
Section cross-reference(s): 1
AB B-cell chronic lymphocytic leukemia (CLL) is characterized by profound immune dysfunction and a marked resistance to apoptosis. In this study, an immortal CLL cell line called WSU-CLL was used to study the characteristics of B-cell CLL as a tumor target for **natural killer** (**NK**), activated **natural killer** , and lymphokine-activated killer (LAK) cells. The WSU-CLL cells were less susceptible to **NK**-cell-mediated cytotoxicity than K562, a std. tumor target cell line. In vitro activation of effector cells with either short-term, low-concn. interleukin-2 or long-term, high-concn. interleukin-2 increased the susceptibility of CLL cells to cell-mediated killing. The addn. of CD1a+/CD3-/CD4+/CD80+/CD83+ dendritic cells derived from human umbilical cord blood increased the cytotoxicity of LAK cells towards WSU-CLL. There was an increased expression of Bcl-2 and decreased expression of Fas on WSU-CLL cells as detd. by RT-PCR techniques, indicating possible roles for these genes in exerting resistance to immune-cell-mediated lysis. When Bcl-2 expression was downregulated in WSU-CLL cells by using gene-specific antisense oligonucleotides, the susceptibility of WSU-CLL cells to the cytotoxicity of the chemotherapeutic agent fludarabine was increased. Thus, the results suggest that in vitro activation with cytokines, addn. of accessory cell populations such as dendritic cells, and/or manipulation of key gene expression, i.e., downregulation of Bcl-2, might be potential strategies for increasing antitumor cytotoxicity to CLL cells.
ST chronic lymphocytic leukemia antitumor immune cell cytokine gene regulation; cytotoxicity immune cell chronic lymphocytic leukemia
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Fas; increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)
IT Immunity
(cell-mediated; increasing the cytotoxicity against B-chronic lymphocytic leukemia by manipulations involving)
IT Antitumor agents
(chronic lymphocytic leukemia; increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations)
IT Cytokines
Interleukin 2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)
IT Fas antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)
IT Lymphocyte

(lymphokine-activated **killer cell**; increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)

IT Lymphocyte
(**natural killer cell**; increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations involving)

IT **21679-14-1**, Fludarabine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations in relation to cytotoxicity of)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

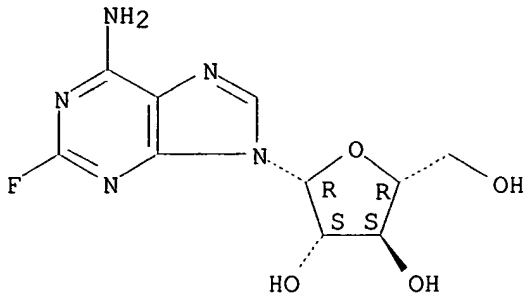
RE

(1) Bandini, G; Bone Marrow Transplant 1991, V7, P251 MEDLINE
(2) Bradley, M; Blood 1998, V92, P4248 HCAPLUS
(3) Buhmann, R; Blood 1999, V93, P1992 HCAPLUS
(4) Caligaris-Cappio, F; Blood Cells 1993, V19, P601 MEDLINE
(5) Caligaris-Cappio, F; Journal of Clinical Oncology 1999, V17, P399408
(6) Cordone, I; Blood 1998, V91, P4342 HCAPLUS
(7) Flinn, I; Semin Oncol 1998, V25, P60 MEDLINE
(8) Foa, R; Blood 1990, V76, P1349 MEDLINE
(9) Foa, R; British Journal of Haematology 1984, V58, P509 MEDLINE
(10) Jewell, A; Leukemia and Lymphoma 1992, V7, P473 MEDLINE
(11) Khouri, I; J Clin Oncol 1994, V12, P748 MEDLINE
(12) Kipps, T; Blood Cells 1998, V19, P615
(13) Kubin, M; European Journal of Immunology 1999, V29, P3466 HCAPLUS
(14) Lee, R; Int Immunol 1996, V8, P991 HCAPLUS
(15) Medvedev, A; Cytokine 1997, V9, P394 HCAPLUS
(16) Michallet, M; Nouv Rev Fr Hematol 1988, V30, P467 MEDLINE
(17) Mohammad, R; Leukemia 1996, V10, P130 MEDLINE
(18) Mohammed, R; Clinical Cancer Research 1998, V4(2), P445
(19) Montserrrat, E; J Intern Med Suppl 1997, V740, P63
(20) Nagata, S; Prog Mol Subcell Biol 1996, V16, P87 HCAPLUS
(21) Oshimi, Y; Journal of Immunology 1996, V157, P2909 HCAPLUS
(22) Panayiotidis, P; Semin Hematol 1999, V36, P171 MEDLINE
(23) Pavletic, Z; Annals of Oncology 1998, V9, P1023 MEDLINE
(24) Pavletic, Z; Bone Marrow Transplantation 2000, V25, P717 MEDLINE
(25) Pepper, C; British Journal of Haematology 1999, V107, P611 HCAPLUS
(26) Platsoucas, C; Journal of Immunology 1980, V125, P1216 MEDLINE
(27) Rao, A; International Journal of Oncology 1997, V11, P281 HCAPLUS
(28) Tefferi, A; Mayo Clin Proc 1992, V67, P457 MEDLINE
(29) Verbik, D; Blood 1985, V85, P1964

IT **21679-14-1**, Fludarabine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing the cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations in relation to cytotoxicity of)

RN 21679-14-1 HCAPLUS
CN 9H-Purin-6-amine, 9-.beta.-D-arabinofuranosyl-2-fluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



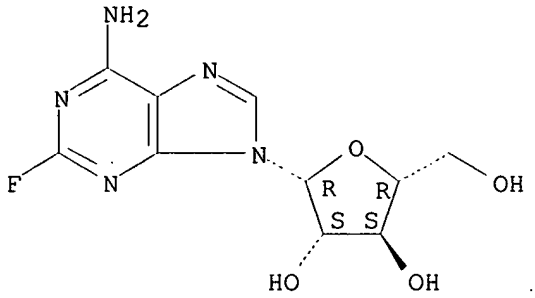
L53 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:115957 HCAPLUS
DN 135:151234
TI Clinical use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation
AU Kalwak, Krzysztof; Ussowicz, Marek; Turkiewicz, Dominik; Ryczan, Renata; Kazanowska, Bernarda; Gorczynska, Ewa; Boguslawska-Jaworska, Janina
CS Department of Pediatric Hematology Oncology, University of Medicine, Wroclaw, 50-345, Pol.
SO Central European Journal of Immunology (**2000**), 25(2), 52-56
CODEN: CJIMFW; ISSN: 1426-3912
PB Termedia
DT Journal
LA English
CC 15-1 (Immunochemistry)
Section cross-reference(s): 4
AB The activity of **natural killer** (**NK**) cells plays an important role in the non-MHC restricted immune response against viral and tumor cells, likewise in the mechanism of "hybrid resistance" leading to graft rejection in HLA-mismatched allogeneic setting. Many assays have been developed to detect **NK** cell cytotoxicity. The most commonly used 51Cr-release assay has several disadvantages, including high cost and potential health hazards due to radioactive probe. Several investigators labeled the membrane of target cells with fluorescent dyes and then measured cell death by propidium iodide (PI) intercalation into DNA of target cells. Thus, we modified non-radioactive flow cytometric method to assess **NK** activity in children undergoing autologous or allogeneic haematopoietic cell transplantation with special regard to monitoring of interleukin-2 (IL-2) adoptive immunotherapy and immune surveillance of patients with congenital immunodeficiencies. After autologous bone marrow/peripheral blood progenitor cell transplant, **NK** cell activity remains impaired. IL-2 might effectively augment immune recovery and control minimal residual disease in circumstances, in which tumor cells might contaminate the graft and remain sensitive to **NK** cells, such as in neuroectodermal tumors. **NK** assay is also of great value in patients with **NK**+ or **NK** - severe combined immunodeficiencies (SCID) and might have clin. implications: **NK**-pos. patients require more aggressive myeloablation and immunosuppression to overcome "hybrid resistance" in haploidentical setting.
ST **natural killer** cytotoxicity assay bone marrow transplantation
IT Transplant and Transplantation
(bone marrow; clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)

IT Development, mammalian postnatal
(child; clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT Cytotoxicity
Hematopoietic precursor cell
(clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT Immunodeficiency
(congenital; clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT Lymphocyte
(**natural killer cell**; clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT Bone marrow
(transplant; clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT 110942-02-4, Proleukin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. use of non-radioactive flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation)
IT 52-24-4, Thiotepa 55-98-1, Busulfan **21679-14-1**, Fludarabine 140608-64-6, OKT-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of flow-cytometric **natural killer cell** cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation and receiving immunosuppressive drugs)
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Atzpodien, J; Oncology 1988, V45, P437 MEDLINE
(2) Brunner, K; Immunology 1968, V14, P181 HCAPLUS
(3) Burdach, S; Adjuvant Proleukin (rIL-2) in Ewing Sarcoma patients with minimal residual disease following bone marrow transplantaion Protocol 1990, EC-RM-027, P1
(4) Chang, L; J Immunol Methods 1993, V16, P45
(5) Garaventa, A; Bone Marrow Transplant 1996, V18, P125 MEDLINE
(6) Hatam, L; Cytometry 1994, V16, P59 MEDLINE
(7) Kalwak, K; Acta Haematol Pol 1999, V30, P215
(8) Ladenstein, R; Bone Marrow Transplant 1995, V15, P697 MEDLINE
(9) Lotzerich, H; J Lab Med 1997, V21, P13
(10) Main, E; J Immunol 1985, V135, P242 MEDLINE
(11) Pession, A; Br J Cancer 1998, V78, P528 HCAPLUS
(12) Phillips, J; J Exp Med 1986, V184, P814
(13) Trincheri, G; Semin Immunol 1995, V7, P83
(14) Yu, Y; Ann Rev Immunol 1993, V10, P189
IT **21679-14-1**, Fludarabine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of flow-cytometric **natural killer cell**

cytotoxicity assay in children undergoing bone marrow or peripheral blood progenitor cell transplantation and receiving immunosuppressive drugs)

RN 21679-14-1 HCAPLUS
CN 9H-Purin-6-amine, 9-.beta.-D-arabinofuranosyl-2-fluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L53 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:344857 HCAPLUS
DN 131:4246
TI Treatment of hematologic disorders
IN Sykes, Megan; Spitzer, Thomas R.
PA The General Hospital Corporation, USA
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K035-14
ICS A61K035-28; A61K035-28; A61K039-395; A61K031-675
CC 15-10 (Immunochemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9925367	A2	19990527	WO 1998-US24209	19981113 <--
	WO 9925367	A3	19990805		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2309919	AA	19990527	CA 1998-2309919	19981113 <--
	EP 1030675	A2	20000830	EP 1998-960199	19981113 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001523645	T2	20011127	JP 2000-520800	19981113 <--
	US 2001048921	A1	20011206	US 1998-191970	19981113 <--
PRAI	US 1997-73230P	P	19971114		
	WO 1998-US24209	W	19981113		

AB The inventors have discovered that hematol. disorders, e.g., both **neoplastic** (hematol. **cancers**) and non-**neoplastic** conditions, can be treated by the induction of mixed chimerism using myeloreductive, but not myeloablative, conditioning. Methods of the invention reduce GVHD, esp. GVHD assocd. with mismatched allogeneic or xenogeneic donor tissue, yet provide, for example, significant

graft-vs.-leukemia (GVL) effect and the like. The method comprises administration of myeloreductive treatment (such as immunosuppressant regimen), introduction of allogeneic donor hematopoietic stem cell to form chimeric bone marrow in the recipient, and an immunosuppressant regimen after donor stem cell introduction to prevent graft-vs.-host response. The immunosuppressant regimen includes depletion of host T lymphocytes and/or **NK** cells by treating with anti-CD4 or CD8 antibodies, anti-thymocyte globulin, anti-lymphoblast globulin, thymic irradn., and cytoreductive agents (e.g. alkylating agents, alkyl sulfonates, nitrosoureas, triazenes, antimetabolites, pyrimidine or purine analogs, vinca alkaloids, epipodophyllotoxins, antibiotics, and others).

ST hematol disorder **cancer** immunosuppressant stem cell transplant

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA, class II; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA-A; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA-B; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA-DR; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HLA; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Erythrocyte
(abnormalities; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Leukemia
(acute myelogenous; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Sulfonates
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(alkanesulfonates; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Transplant and Transplantation
(allotransplant; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

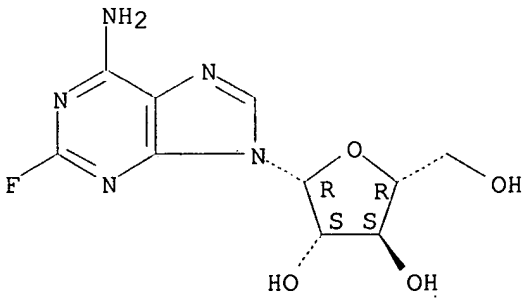
IT Nutrients
(anti-; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)

IT Anemia (disease)
(aplastic; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Transplant and Transplantation
Transplant and Transplantation
(bone marrow; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Cord blood
(cells; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Leukemia
(chronic lymphocytic; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Leukemia
(chronic myelocytic; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT T cell (lymphocyte)
(depletion; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Blood
(disease; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Immunity
(disorder, inherited; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Lymphoblast
(globulin; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Transplant and Transplantation
(graft-vs.-host reaction; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Leukemia
(graft-vs.-leukemia; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Lymphoma
(graft-vs.-lymphoma; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT **Neoplasm**
(hematol.; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Alkylating agents, biological
Antibiotics
Hodgkin's disease
Immunosuppressants
Multiple myeloma
Myelodysplastic syndromes
Sickle cell anemia
Thalassemia
Thymus gland
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic

stem cell transplantation for treatment of hematol. disorders)
IT CD4 (antigen)
CD8 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Leukemia
(lymphocytic; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Hemoglobins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic disorders, hemoglobinopathy; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, OKT3 and LO-CD2a and others; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Lymphocyte
(**natural killer cell**, depletion;
immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Lymphoma
(non-Hodgkin's; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Blood cell
(peripheral; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Chemotherapy
(refractory; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Hematopoietic precursor cell
(stem, transplant; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Radiation
(thymic; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Globulins, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thymocyte or lymphoblast; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Thymus gland
(thymocyte, globulin; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Bone marrow
Bone marrow
Leukocyte
(transplant; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol.

disorders)
IT Alkaloids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vinca; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT Transplant and Transplantation
(xenotransplant; immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT 4375-07-9, Epipodophyllotoxin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT 50-18-0, Cyclophosphamide 50-76-0, Dactinomycin 51-21-8, Fluorouracil 51-75-2, Mechlorethamine 52-24-4, Thiotepa 55-86-7D, Nitrogen mustard, derivs. 55-93-6, Dimethyl myleran 55-98-1, Busulphan 57-22-7, Vincristine 59-05-2, Methotrexate 59-30-3D, Folic acid, derivs. 120-73-0D, Purine, derivs. 147-94-4, Cytarabine 148-82-3, Melphalan 154-42-7, Thioguanine 154-93-8, Carmustine 289-95-2D, Pyrimidine, derivs. 305-03-3, Chlorambucil 488-41-5 865-21-4, Vinblastine 1404-00-8, Mitomycin 4342-03-4, Dacarbazine 11056-06-7, Bleomycin 13010-20-3D, Nitrosourea, derivs. 13010-47-4, Lomustine 13909-09-6, Semustine 15056-34-5D, Triazene, derivs. 18378-89-7, Plicamycin 18883-66-4, Streptozotocin 20830-81-3, Daunorubicin **21679-14-1**, Fludarabine 23214-92-8, Doxorubicin 29767-20-2, Teniposide 31441-78-8, Mercaptopurine 33419-42-0, Etoposide 53643-48-4, Vindesine 58957-92-9, Idarubicin 89149-10-0, Deoxyspergualin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
IT **21679-14-1**, Fludarabine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant regimen and allogeneic or xenogeneic hematopoietic stem cell transplantation for treatment of hematol. disorders)
RN 21679-14-1 HCAPLUS
CN 9H-Purin-6-amine, 9-.beta.-D-arabinofuranosyl-2-fluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

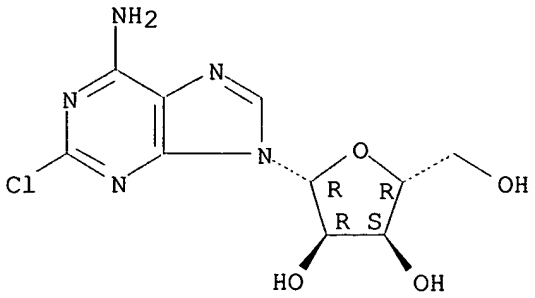


L53 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:345385 HCAPLUS
DN 127:44599
TI 2-Chloroadenosine stimulates granule exocytosis from mouse **natural killer cells**: evidence for signal transduction through a novel extracellular receptor
AU Williams, Brent A.; Blay, Jonathan; Hoskin, David W.
CS ep. of Microbiol. and Immunol., Dalhousie Univ., Halifax, NS, B3H 4H7,

Can.
SO Experimental Cell Research (**1997**), 233(1), 187-197
CODEN: ECREAL; ISSN: 0014-4827
PB Academic
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): 15
AB The effect of 2-chloroadenosine (2CA), an adenosine receptor agonist, on the activation status of mouse **natural killer** (**NK**) cells was detd. Splenic lymphocytes incubated with 2CA exocytosed an **NK** cell-assocd. granzyme with N.alpha.-CBZ-L-lysine thiobenzyl ester (BLT) esterase activity in a dose- and time-dependent manner. Selective depletion of **NK** cells by anti-asialoGM1 antibody plus complement pretreatment confirmed that **NK** cells were the source of the BLT esterase activity. 2CA-induced granule exocytosis was not reduced in the presence of the nucleoside uptake blockers NBTI, dilazep, or dipyridamole, indicating the involvement of an extracellular receptor. However, adenosine or other A1, A2, or A3 cell-surface adenosine receptor agonists failed to trigger the exocytotic process. Furthermore, the nonselective adenosine receptor antagonist theophylline, as well as the selective A1 receptor antagonist DPCPX and the selective A2 receptor antagonist DMPX, did not interfere with 2CA-induced BLT esterase secretion. These data suggest that 2CA acts on **NK** cells via a novel (non-A1/A2/A3) cell-surface receptor. Genistein, a protein tyrosine kinase inhibitor, and calphostin C, a protein kinase C inhibitor, both interfered with 2CA-induced granule exocytosis. Pertussis toxin, an ADP-ribosylating toxin to which certain GTP-binding proteins are sensitive, also inhibited 2CA-stimulated BLT esterase release. In addn., 2CA-induced granule exocytosis was reduced in the presence of cyclosporin A, an inhibitor of Ca2+-dependent signaling pathways, and the Ca2+-chelating agent EGTA. We conclude that 2CA, acting through a novel extracellular receptor on mouse **NK** cells, triggers granule exocytosis via a Ca2+-dependent signal transduction pathway that is coupled to GTP-binding proteins and involves protein tyrosine kinase and protein kinase C activation.
ST **natural killer cell** exocytosis chloroadenosine
IT Exocytosis
Signal transduction, biological
(2-chloroadensoine triggering of **natural killer cell** exocytosis through novel extracellular receptor)
IT Lymphocyte
(**natural killer cell**; 2-chloroadensoine triggering of **natural killer cell** exocytosis through novel extracellular receptor)
IT **146-77-0**, 2-Chloroadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(2-chloroadensoine triggering of **natural killer cell** exocytosis through novel extracellular receptor)
IT 7440-70-2, Calcium, biological studies 80449-02-1, Protein tyrosine kinase 141436-78-4, Protein kinase C
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(2-chloroadensoine triggering of **natural killer cell** exocytosis through novel extracellular receptor)
IT **146-77-0**, 2-Chloroadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(2-chloroadensoine triggering of **natural killer cell** exocytosis through novel extracellular receptor)
RN 146-77-0 HCAPLUS

CN Adenosine, 2-chloro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L53 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:206326 HCAPLUS
DN 122:211874
TI 2-Chloroadenosine inhibits the MHC-unrestricted cytolytic activity of anti-CD3-activated **killer cells**: evidence for the involvement of a non-A1/A2 cell-surface adenosine receptor
AU Hoskin, David W.; Reynolds, Teresa; Blay, Jonathan
CS Faculty of Medicine, Dalhousie University, Halifax, NS, B3H 4H7, Can.
SO Cellular Immunology (**1994**), 159(1), 85-93
CODEN: CLIMB8; ISSN: 0008-8749
PB Academic
DT Journal
LA English
CC 15-8 (Immunochemistry)
Section cross-reference(s): 1
AB Adenosine is likely to be a frequent constituent of the **tumor** microenvironment since this purine nucleoside is produced in quantity by hypoxic cells such as those found in the interior of poorly vascularized solid **tumors**. In this study the authors show that 2-chloroadenosine (2CA), a stable analog of adenosine, inhibits, in a dose-dependent fashion, MHC-unrestricted killing of P815 **tumor** target cells by anti-CD3-activated killer (AK) lymphocytes. 2CA mediates this effect by interfering with the recognition/adhesion phase of cytolysis. Blocking cellular uptake of 2CA with dipyridamole, rather than attenuating the inhibitory effect, potentiated the inhibition of cytolysis, indicating the involvement of a cell-surface receptor. However, neither the A1 receptor antagonist DPCPX, nor the A2 receptor antagonist DMPX were able to block the inhibitory effect of 2CA on AK lymphocyte function. Similarly, the nonselective A1 and A2 receptor antagonists, theophylline and 8-phenyltheophylline, had no effect on 2CA-mediated inhibition of AK cell activity. Taken together, these data provide evidence that 2CA inhibits the cytolytic activity of AK lymphocytes by interacting with a novel non-A1/A2 cell-surface receptor. A similar effect mediated in vivo by **tumor**-elaborated adenosine may be involved in **tumor**-assocd. immunosuppression.
ST chloroadenosine **killer cell** cytolysis adenosine receptor; **cancer** immunosuppression adenosine analog
IT Cell membrane
(chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes in relation to cell-surface adenosine receptors antagonists)
IT **Neoplasm**
(**tumor**-assocd. immunosuppression; chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes)
IT Immunosuppression

(**tumor**-assocd.; chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes)

IT Lymphocyte
(**killer cell**, chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes)

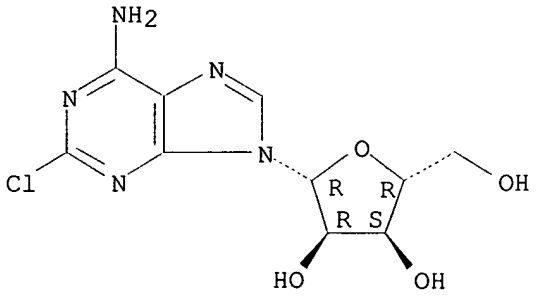
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(purinergic, chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes in relation to cell-surface adenosine receptors antagonists)

IT **146-77-0**, 2-Chloroadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes)

IT **146-77-0**, 2-Chloroadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(chloroadenosine effect on the oncolytic function of anti-CD3-activated killer lymphocytes)

RN 146-77-0 HCAPLUS
CN Adenosine, 2-chloro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L53 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:545035 HCAPLUS
DN 113:145035
TI Adenosine receptors and modulation of **natural killer cell** activity by purine nucleosides
AU Priebe, Teresa; Platsoucas, Chris D.; Nelson, J. Arly
CS M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SO Cancer Research (**1990**), 50(14), 4328-31
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
CC 1-7 (Pharmacology)
AB **Natural killer** (**NK**) cell activity is inhibited in vivo by the adenosine analog tubercidin (Tub) and stimulated by the deoxyadenosine analog 2-fluoro-1-.beta.-D-arabinofuranosyladenine 5'-monophosphate (F-ara-AMP) in the spleen lymphocytes from mice. The inhibition by Tub and stimulation by F-ara-AMP of **NK** cell activity are readily demonstrable in murine and human lymphocytes exposed to the drugs in vitro. In mouse spleen lymphocytes, **NK** cell activity is also inhibited by adenosine receptor A2 agonists, whereas potent A1 receptor agonists are more effective stimulators. Inhibition produced by adenosine, deoxyadenosine, and adenosine receptor agonists, but not by Tub, is partially prevented by the adenosine receptor antagonist 1,3-dipropyl-8-phenylxanthine amine congener. Agents that

stimulate **NK** cell activity (deoxyadenosine, A1 receptor agonists, F-ara-AMP) do not increase further the 1.5-fold enhancement produced by a 10-6M 1,3-dipropyl-8-phenylxanthine amine congener. The nucleoside transport inhibitor p-nitrobenzylthioinosine 5'-monophosphate has no effect on **NK** cell activity or intracellular ribonucleotide pools; however, it partially prevents Tub 5'-triphosphate formation, ATP depletion, and **NK** cell inhibition in mouse spleen cells treated with Tub. Nitrobenzylthioinosine 5'-monophosphate also partially prevents the F-ara-AMP stimulation of **NK** cell activity, but it does not influence the effects of adenosine or deoxyadenosine. The results obtained with the adenosine receptor agonists suggest roles for both A1 and A2 receptors in regulating murine **NK** cell activity. Tub inhibition of **NK** cell activity does not involve adenosine receptors; however, inhibition by the other agents may be mediated via an A2 receptor (stimulatory for adenylyl cyclase). Since p-nitrobenzylthioinosine 5'-monophosphate inhibited the stimulation of **NK** cell activity by F-ara-AMP, this stimulation may occur via an intracellular P site (inhibitory to adenylyl cyclase).

ST killer lymphocyte adenosine receptor purine nucleoside; splenocyte killer adenosine receptor purine nucleoside

IT Lymphocyte
(**natural killer**, of spleen, adenine nucleosides effects on, adenosine receptors mediation of)

IT Receptors
RL: BIOL (Biological study)
(purinergic A1, splenocyte **natural killer** activity response to adenine nucleosides mediation by)

IT Receptors
RL: BIOL (Biological study)
(purinergic A2, splenocyte **natural killer** activity response to adenine nucleosides mediation by)

IT Spleen
(splenocyte, **natural killer** activity of, adenine nucleosides effect on, adenosine receptors mediation of)

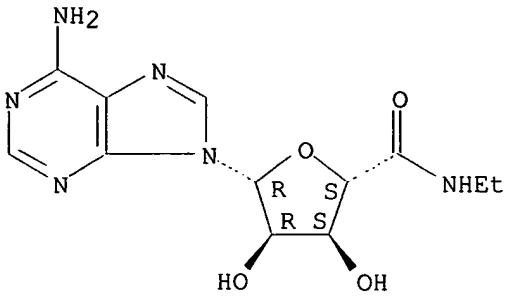
IT 58-61-7, Adenosine, biological studies 69-33-0, Tubercidin 73-24-5D, Adenine, nucleotides 958-09-8, Deoxyadenosine **35920-39-9**, 5'-N-Ethylcarboxamidoadenosine 38594-97-7 41552-82-3, N6-Cyclopentyladenosine 53296-10-9, 2-Phenylaminoadenosine 65199-10-2 96865-92-8 129576-22-3
RL: BIOL (Biological study)
(splenocyte **natural killer** activity modulation by, adenosine receptors in)

IT **35920-39-9**, 5'-N-Ethylcarboxamidoadenosine
RL: BIOL (Biological study)
(splenocyte **natural killer** activity modulation by, adenosine receptors in)

RN 35920-39-9 HCAPLUS

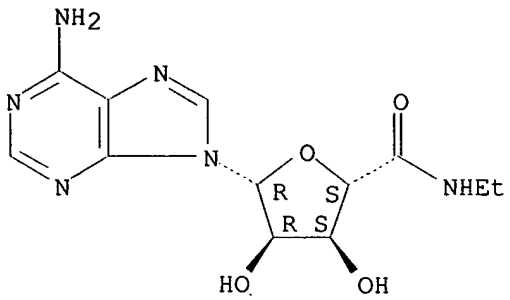
CN .beta.-D-Ribofuranuronamide, 1-(6-amino-9H-purin-9-yl)-1-deoxy-N-ethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




```
=> fil reg
FILE 'REGISTRY' ENTERED AT 16:48:44 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 OCT 2002  HIGHEST RN 463296-69-7
DICTIONARY FILE UPDATES:  20 OCT 2002  HIGHEST RN 463296-69-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d l45 ide can tot

L45  ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2002 ACS
RN   35920-39-9  REGISTRY
CN   .beta.-D-Ribofuranuronamide, 1-(6-amino-9H-purin-9-yl)-1-deoxy-N-ethyl-
     (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   5'-N-Ethylcarboxamidoadenosine
CN   5'-N6-Ethylcarboxamidoadenosine
CN   744-96
CN   Adenosine 5'-ethylcarboxamide
CN   Adenosine 5'-N-ethylcarboxamide
CN   D-NECA
CN   NECA
FS   STEREOSEARCH
DR   74992-42-0, 84272-21-9, 100111-00-0, 110282-65-0
MF   C12 H16 N6 O4
CI   COM
LC   STN Files:   AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
       CANCERLIT, CAPLUS, CASREACT, CHEMCATS, DDFU, DRUGU, EMBASE, IFICDB,
       IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
```

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1051 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1051 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:226896

REFERENCE 2: 137:210830

REFERENCE 3: 137:180158

REFERENCE 4: 137:136577

REFERENCE 5: 137:135364

REFERENCE 6: 137:119953

REFERENCE 7: 137:103775

REFERENCE 8: 137:103378

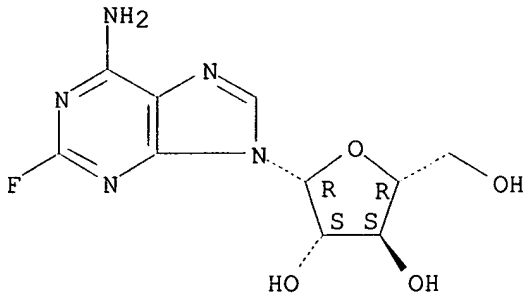
REFERENCE 9: 137:73118

REFERENCE 10: 137:28521

L45 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **21679-14-1** REGISTRY
CN 9H-Purin-6-amine, 9-.beta.-D-arabinofuranosyl-2-fluoro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenine, 9-.beta.-D-arabinofuranosyl-2-fluoro- (8CI)
OTHER NAMES:
CN 2-Fluoro-9-.beta.-D-arabinofuranosyladenine
CN 9-.beta.-D-Arabinofuranosyl-2-fluoroadenine
CN 9-.beta.-D-Arabinosyl-2-fluoroadenine
CN F-ara-A
CN Fludarabine
CN NSC 118218
CN NSC 118218H
FS STEREOSEARCH
MF C10 H12 F N5 O4
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES,

EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

530 REFERENCES IN FILE CA (1962 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
531 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:247550

REFERENCE 2: 137:231369

REFERENCE 3: 137:227069

REFERENCE 4: 137:226367

REFERENCE 5: 137:226341

REFERENCE 6: 137:226339

REFERENCE 7: 137:226332

REFERENCE 8: 137:226313

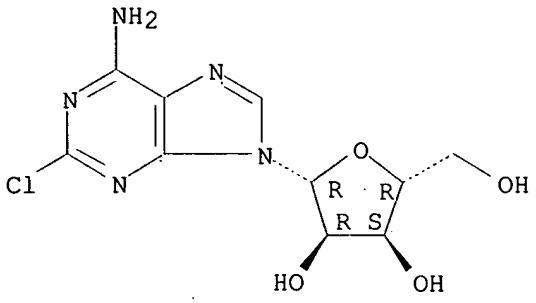
REFERENCE 9: 137:226114

REFERENCE 10: 137:215809

L45 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **146-77-0** REGISTRY
CN Adenosine, 2-chloro- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Chloro-D-adenosine
CN 2-Chloroadenosine
CN Antibiotic AT 265B
FS STEREOSEARCH
MF C10 H12 Cl N5 O4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE,

RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1059 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1059 REFERENCES IN FILE CAPLUS (1962 TO DATE)
14 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:242064

REFERENCE 2: 137:195227

REFERENCE 3: 137:164035

REFERENCE 4: 137:134919

REFERENCE 5: 137:119944

REFERENCE 6: 137:57851

REFERENCE 7: 137:28521

REFERENCE 8: 136:366120

REFERENCE 9: 136:319688

REFERENCE 10: 136:303902

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 17:02:20 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 21 Oct 2002 VOL 137 ISS 17
FILE LAST UPDATED: 20 Oct 2002 (20021020/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d all hitstr tot

L96 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:512807 HCAPLUS
DN 135:302734
TI Attempted reconstruction of the immune system using low doses of interleukin 2 in chronic lymphocytic leukemia patients treated with 2-chlorodeoxyadenosine: Results of a pilot study
AU Dmoszynska, Anna; Legiec, Wojciech; Wach, Malgorzata
CS Department Of Hematology, University School of Medecine, Lublin, 20090, Pol.
SO Leukemia & Lymphoma (**1999**), 34(3/4), 335-340
CODEN: LELYEA; ISSN: 1042-8194
PB Harwood Academic Publishers
DT Journal
LA English
CC 15-8 (Immunochemistry)
Section cross-reference(s): 1
AB This study was designed to investigate the immunostimulatory effect of low dose IL-2 treatment in B-CLL patients previously treated with 2-chlorodeoxyadenosine (2CdA) in whom severe depletion of T lymphocyte subsets was obsd. Four patients enrolled into the study had previously been treated with 3-6 courses of 2 CdA. All patients suffered from recurrent infections and showed CD4+ and CD8+ immunosuppression. Recombinant IL-2 was given s.c. at a dose of 100 .mu.g (1.8 .times. 106IU) daily for 6 wk. The drug was administered between 2CdA courses. These preliminary studies showed a marked increase in T cell subsets after IL-2 treatment. All patients displayed an increase of **NK cells** and there was increased expression of IL-2 receptors (CD 25 and CD 122) on lymphocytes. It is possible that the combination of cytotoxic therapy with 2CdA and low dose rIL-2 could stimulate the T-cell immune system and may be a promising regimen in patients with B-CLL with severe depletion in T-cell subsets.
ST interleukin 2 chlorodeoxyadenosine immunosuppression lymphocytic leukemia
IT **CD4-positive T cell**
CD8-positive T cell
Immunostimulants
(attempted reconstruction of immune system using low doses of interleukin 2 in humans with chronic lymphocytic leukemia treated with 2-chlorodeoxyadenosine)
IT Interleukin 2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attempted reconstruction of immune system using low doses of interleukin 2 in humans with chronic lymphocytic leukemia treated with 2-chlorodeoxyadenosine)
IT Antitumor agents
(chronic lymphocytic leukemia; attempted reconstruction of immune

system using low doses of interleukin 2 in humans with chronic lymphocytic leukemia treated with 2-chlorodeoxyadenosine)

IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attempted reconstruction of immune system using low doses of interleukin 2 in humans with chronic lymphocytic leukemia treated with 2-chlorodeoxyadenosine)

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

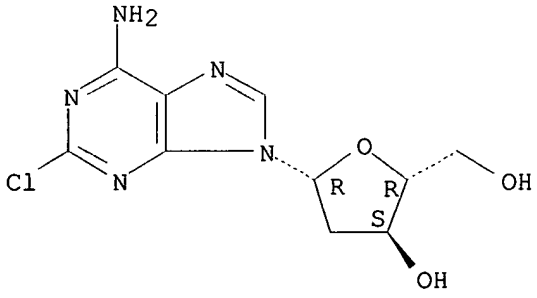
(1) De Paoli, P; J Clin Invest 1997, V100, P2737 HCAPLUS
(2) Dmoszynska, A; Acta Haematol Pol 1998, V29, P45
(3) Dmoszynska, A; Brit J Haemat 1998, V102, P82
(4) Fenchel, K; Brit J Haemat 1998, V102, P89
(5) Ghezzi, S; J Biol Regul Homeost Agent 1997, V11, P74 MEDLINE
(6) Haenninen, E; Cancer Research 1991, V50, P63312
(7) Haeusler, M; Brit J Haemat 1998, V102, P88
(8) Juliusson, G; Hematol Cell Ther 1997, V39, P541
(9) Juliusson, G; J Clin Oncol 1993, V11, P570
(10) Kandefer-Szerszen, M; Arch Immunol Ther Exp 1998, V45, P177
(11) Knauf, W; Hematol Cell Ther 1997, V39, P588
(12) Kumar, A; J Clin Invest 1996, V97, P1219 HCAPLUS
(13) O'Brien, S; Hematol Cell Ther 1997, V39, P43
(14) Peest, D; Brit J Haemat 1995, V89, P328 MEDLINE
(15) Robak, T; Leuk Lymph V18, P179 MEDLINE
(16) Rolinski, J; Annales Univ M Curie-Sklodowska 1996, V51, P143
(17) Seymour, J; Leukemia 1995, V9, P929 MEDLINE
(18) Von Rohr, A; Proceedings of ASCO 1997, V17, P18a

IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attempted reconstruction of immune system using low doses of interleukin 2 in humans with chronic lymphocytic leukemia treated with 2-chlorodeoxyadenosine)

RN 4291-63-8 HCAPLUS

CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:698703 HCAPLUS

DN 132:77394

TI 3'-Deoxy-3'-fluoro analogs of 2-5A core trimers: their effect on the lytic activity of human NK lymphocytes

AU Kalinichenko, E. N.; Podkopaeva, T. L.; Kelve, M.; Saarma, M.; Mikhailopulo, I. A.

CS Institute of Bioorganic Chemistry, Belorussian Academy of Sciences, Minsk, 220141, Belarus

SO Bioorganicheskaya Khimiya (**1999**), 25(4), 282-289

CODEN: BIKHD7; ISSN: 0132-3423
PB MAIK Nauka
DT Journal
LA Russian
CC 15-5 (Immunochemistry)
Section cross-reference(s): 14

AB The effect of core trimers, (2'-5')-analogs of oligoadenylic acid contg. 9-(3'-deoxy-3'-fluoro-.beta.-D-xylofuranosyl)adenine (AF) and 3'-deoxy-3'-fluoroadenosine (AF) in various positions of the oligomer chain, on the lytic activity of human **natural killer cells** (**NK cells**) was studied. It was shown that all fluorodeoxy analogs enhance the lytic activity of intact NK lymphocytes, which follows from the lysis rate const. k2. The substitution of either the central adenosine fragment or the 5'-terminal residue of (2'-5')A3 with AF causes a decrease in the no. of active **NK cells**, which, unlike the case of the **natural** core trimer, leads to a loss of the capacity to increase the activity of NK. Isomeric ribo- analogs, (2'-5')(AF)A2 and(2'-5')A(AF)A, and trimers with the 2'(3')-terminal nucleotide substituted by AF or AF increased the activity of **NK cells** with an effectiveness close to or higher than the **natural** trimer (2'-5')A3. Because isomeric xylo- and ribo-3'-deoxy-3'-fluoro analogs of (2'-5')A3 are stereochem. modified oligomers, this study shows that the stereostructure of these trimers affects the increase of the lytic activity of **NK cells**.

ST deoxyfluoro core trimer cytotoxicity human **natural killer** lymphocyte; deoxyfluoroadenine core trimer cytotoxicity; deoxyfluoroadenosine core trimer cytotoxicity; **natural killer cell** lymphocyte core trimer deoxyfluoroadenine deoxyfluoroadenosine; adenosine deoxyfluoro core trimer cytotoxicity; adenine deoxyfluoro core trimer cytotoxicity

IT Cytotoxicity
(effect of deoxyfluoro analogs of core trimers on the cytotoxicity of human nk lymphocytes)

IT Oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(fluorinated; effect of deoxyfluoro analogs of core trimers on the cytotoxicity of human nk lymphocytes)

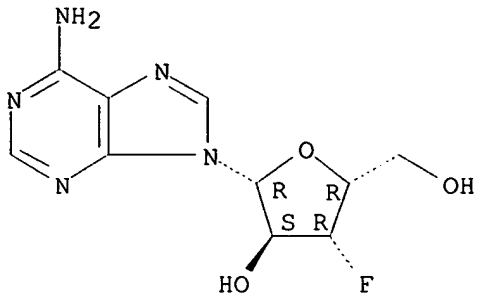
IT **Lymphocyte**
(**natural killer cell**; effect of deoxyfluoro analogs of core trimers on the cytotoxicity of human nk lymphocytes)

IT 58-61-7, Adenosine, biological studies **20535-16-4** 70062-83-8 **75059-22-2** 155173-76-5 155173-77-6 155173-78-7 155173-79-8 155173-80-1 155173-81-2 155173-82-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of deoxyfluoro analogs of core trimers on the cytotoxicity of human nk lymphocytes)

IT **20535-16-4 75059-22-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of deoxyfluoro analogs of core trimers on the cytotoxicity of human nk lymphocytes)

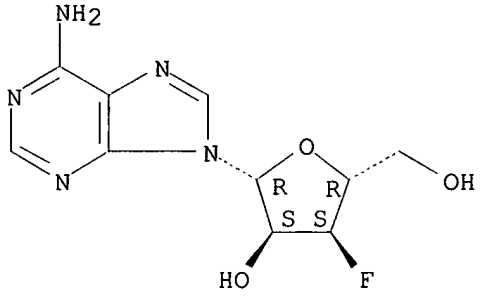
RN 20535-16-4 HCAPLUS
CN 9H-Purin-6-amine, 9-(3-deoxy-3-fluoro-.beta.-D-xylofuranosyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 75059-22-2 HCAPLUS
CN Adenosine, 3'-deoxy-3'-fluoro- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:57784 HCAPLUS
DN 128:212783
TI Ex vivo evidence of lymphocyte apoptosis in hairy cell leukemia, induced by 2-chlorodeoxyadenosine treatment
AU Idink-Mecking, C. A. M.; Richel, D. J.; Vermes, I.; Schaafsma, M. R.; Reutelingsperger, C.; Haanen, C.
CS Medical Spectrum Twente, Department of Internal Medicine, Hospital Group Enschede, Neth.
SO Annals of Hematology (**1998**), 76(1), 25-29
CODEN: ANHEE8; ISSN: 0939-5555
PB Springer-Verlag
DT Journal
LA English
CC 1-6 (Pharmacology)
AB In all living cells phosphatidylserine (PS) is located at the cytosol side of the membrane and becomes exposed at the cell surface only during necrosis or apoptosis. This phenomenon allows measurements of cell death on a cell-by-cell basis, using labeled annexin V, which has a strong affinity to PS. Two patients with hairy cell leukemia (HCL) who had relapsed after splenectomy and .alpha.-interferon therapy were treated with 2-chlorodeoxyadenosine (2-CdA) for 7 days. Blood samples were taken from the start of therapy until day 22. Percentages of HCL cells, T cells, B cells, and **NK cells** were measured with PE-labeled monoclonal antibodies by flow cytometry (FCM). The abs. lymphocyte count dropped rapidly to almost zero in both patients within 7 days. The disappearance rate of lymphocyte subfractions did not show a specific pattern. The percentage of apoptosis in lymphocyte subfractions was measured in freshly prepd. cell samples by FCM with FITC-labeled annexin V in the propidium iodide-neg. (non-necrotic) cell fraction.

Percentages of PS-pos. cells increased gradually untill a nadir of annexin V positivity was reached at 14 and 16 days. Because during the first week the abs. cell counts became almost zero, the abs. nos. of PS-pos. cells were still extremely low (<108/L). Apoptotic cells were obsd. in circulation after the 2-CdA therapy.

ST hairy cell leukemia apoptosis chlorodeoxyadenosine antitumor

IT Leukemia
(hairy-cell; lymphocyte apoptosis in hairy cell leukemia induced by 2-chlorodeoxyadenosine antitumor treatment in humans)

IT Antitumor agents
Apoptosis
Lymphocyte
(lymphocyte apoptosis in hairy cell leukemia induced by 2-chlorodeoxyadenosine antitumor treatment in humans)

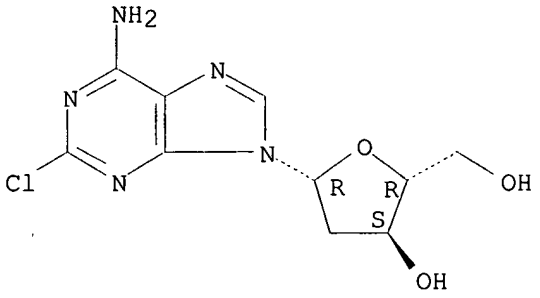
IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lymphocyte apoptosis in hairy cell leukemia induced by 2-chlorodeoxyadenosine antitumor treatment in humans)

IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lymphocyte apoptosis in hairy cell leukemia induced by 2-chlorodeoxyadenosine antitumor treatment in humans)

RN 4291-63-8 HCAPLUS

CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2002 ACS

AN 1997:752734 HCAPLUS

DN 128:3889

TI Preparation of lipophilic oligopeptides with immunomodulating activity

IN Penney, Christopher; Zacharie, Boulos

PA Biochem Pharma Inc., Can.

SO U.S., 15 pp., Cont.-in-part of U.S. Ser. No. 917,464, abandoned.
CODEN: USXXAM

DT Patent

LA English

IC ICM A61K038-00

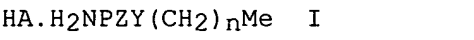
NCL 514019000

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 15, 63

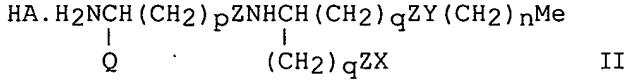
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5688771	A	19971118	US 1994-313304	19941003 <--
	ZA 9302282	A	19931018	ZA 1993-2282	19930330 <--
	WO 9320100	A1	19931014	WO 1993-CA144	19930402 <--

W: AU, CA, HU, JP, NZ, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
PRAI US 1992-862694 19920403
US 1992-917464 19920721
WO 1993-CA144 19930402
OS MARPAT 128:3889
GI



I



II

AB New, small and structurally simple immunomodulating oligopeptides I [Z = CO, CS; Y = linker appropriate to connect alkyl chain to Z, such as O, S, NH; n = 11-19; HA = absent, org. or inorg. acid forming physiol. acceptable salt; P = oligopeptide contg. 2-5 amino acids independently linked by amide or thioamide bonds] and II [p = 0-4; each Z = CO, CS; each q = 0-2; Y, n, HA = as above; X = NH2, OH, OMe; Q = C1-4 (un)branched alkyl, Ph, benzyl, hydroxymethyl, or **naturally** occurring amino acid side chain] are disclosed. The oligopeptides of this invention possess a long, lipophilic alkyl chain. These immunomodulating oligopeptides can be used in conjunction with antiviral or anticancer agents in the treatment of human and animal diseases. Processes for the syntheses of immunomodulating chems. are also disclosed. Thus, D-alanyl-L-glutamine octadecyl ester hydrochloride (BCH 527) was prepd. via std. esterification, peptide coupling, and deprotection steps. BCH 527 and related lipopeptides were tested for immunomodulating activity on **natural killer cell** activity in normal and influenza virus-infected C57BL/6 mice. BCH 527 was also tested for antiviral activity against cytomegalovirus in infected mice.

ST lipophilic oligopeptide prepn immunomodulator; antiviral agent lipophilic oligopeptide prepn; anticancer agent lipophilic oligopeptide prepn; antibacterial agent lipophilic oligopeptide prepn

IT Antibacterial agents
Antitumor agents
Antiviral agents
Cytomegalovirus
Immunomodulators
Influenza
(prepn. of lipophilic oligopeptides with immunomodulating activity)

IT Lipopeptides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

IT 153116-76-8P 153508-67-9P, BCH 523 153508-68-0P, BCH 525
153508-69-1P, BCH 1315 153508-70-4P, BCH 1316 153508-71-5P, BCH 1317
153508-72-6P, BCH 1318 153508-73-7P, BCH 276 153508-74-8P, BCH 527
153508-75-9P, BCH 526 153508-76-0P, BCH 524 153508-77-1P, BCH 1325
153508-78-2P, BCH 1319 153508-79-3P, BCH 1320 153508-80-6P, BCH 1321
153508-81-7P, BCH 1322 153508-82-8P, BCH 1323 153508-83-9P, BCH 1326
153508-84-0P, BCH 1375 153508-85-1P, BCH 1376 153508-86-2P, BCH 1373
153538-42-2P, BCH 1365 198548-18-4P 198548-19-5P 198548-20-8P
198548-21-9P 198548-22-0P 198548-23-1P 198548-24-2P 198548-25-3P
198548-26-4P 198548-27-5P 198548-28-6P 198548-29-7P 198548-30-0P
198548-31-1P 198548-32-2P 198548-33-3P 198548-34-4P 198548-35-5P

198754-32-4P 198754-33-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

IT 54-42-2, 5-Iododeoxyuridine 768-94-5, Tricyclo[3.3.1.13,7]decan-1-amine **4097-22-7**, 2',3'-Dideoxyadenosine 4428-95-9, Foscarnet 7481-89-2, 2',3'-Dideoxycytidine 30516-87-1, Azidothymidine 36791-04-5, Ribavirin 59277-89-3, Acyclovir 69655-05-6, 2',3'-Dideoxyinosine 82410-32-0, Ganciclovir 118353-05-2, Carbovir 134678-17-4, 3TC
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

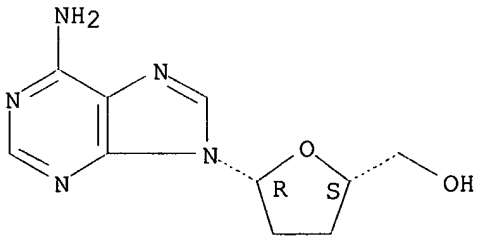
IT 56-40-6, Glycine, reactions 112-92-5, Octadecanol 124-30-1, Octadecylamine 2592-18-9 2900-27-8, N-tert-Butoxycarbonyl-L-phenylglycine 3262-72-4 6368-20-3 13574-13-5 13734-41-3 15761-38-3 16937-92-1 18814-50-1 22838-58-0 33125-05-2, Boc-D-Phg-OH 35793-73-8 50515-48-5 59481-76-4 61348-28-5 104719-63-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

IT 59404-67-0P, Glycine octadecyl ester hydrochloride 153508-45-3P 153508-46-4P 153508-47-5P 153508-48-6P 153508-49-7P 153508-50-0P 153508-51-1P 153508-54-4P 153508-55-5P 153508-56-6P 153508-57-7P 153508-58-8P 153508-59-9P 153508-60-2P 153508-61-3P 153508-62-4P 153508-63-5P 153508-64-6P 153508-65-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

IT **4097-22-7**, 2',3'-Dideoxyadenosine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. of lipophilic oligopeptides with immunomodulating activity)

RN 4097-22-7 HCAPLUS
CN Adenosine, 2',3'-dideoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

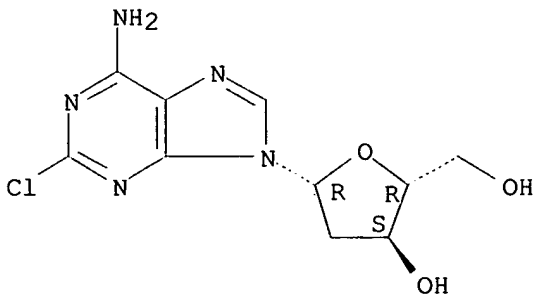
Absolute stereochemistry. Rotation (+).



L96 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:144394 HCAPLUS
DN 127:75682
TI T cells and **natural killer cells** after treatment of hairy cell leukemia with 2-chlorodeoxyadenosine
AU Schirmer, Michael; Hilbe, Wolfgang; Geisen, Francoise; Thaler, Josef; Konwalinka, Guenther
CS Department Internal Medicine, University Hospital Innsbruck, Innsbruck, A-6020, Austria
SO Acta Haematologica (**1997**), 97(3), 180-183
CODEN: ACHAAH; ISSN: 0001-5792
PB Karger

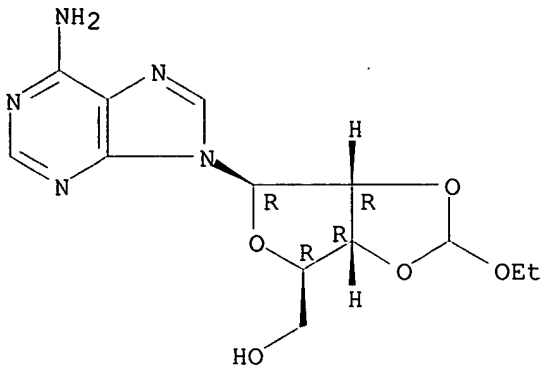
DT Journal
LA English
CC 1-6 (Pharmacology)
AB More than 6 mo after treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA), continuous suppression of CD4+ lymphocyte subsets did not lead to an increased rate of infections. **Natural killer cells** increased to 203 cells/.mu.L during the following 4 mo, whereas CD3+ an CD4+ T cell subsets did not reach pretreatment levels even more than 1 yr after 2-CdA therapy. No severe infections were registered after the early leukopenic phase of 2 wk after treatment.
ST hairy cell leukemia chlorodeoxyadenosine CD antigen; lymphocyte **natural killer cell** chlorodeoxyadenosine leukemia
IT Immunoglobulin receptors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(IgG type III; T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
IT **T cell (lymphocyte)**
(T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
IT CD3 (antigen)
CD4 (antigen)
CD8 (antigen)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
IT Leukemia
(hairy-cell; T cells and **natural killer cells** after treatment of hairy cell leukemia with 2-chlorodeoxyadenosine)
IT **Lymphocyte**
(**natural killer cell**; T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(T cells and **natural killer cells** in hairy cell leukemia after 2-chlorodeoxyadenosine)
RN 4291-63-8 HCAPLUS
CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



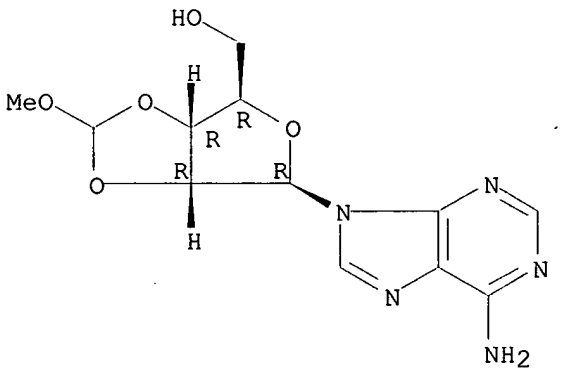
L96 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:531115 HCAPLUS
DN 119:131115
TI Immunostimulating activity of 5'-phosphonates of nucleosides
AU Pisarev, V. M.; Tarusova, N. B.; Georgiyev, B. P.; Tutelyan, A. V.; Leskov, V. P.; Kremlev, S. G.; Atrazheva, Ye. D.; Pevnitsky, L. A.
CS Inst. Genet. Chelov., Moscow, Russia
SO Khimiko-Farmatsevticheskii Zhurnal (**1992**), 26(7-8), 4-9
CODEN: KHFZAN; ISSN: 0023-1134
DT Journal
LA Russian
CC 1-7 (Pharmacology)
AB The study was undertaken to examine the immunomodulating activity of new nucleosides and their nucleotide analogs (5'-phosphonates) with conformational limitations of the ribose ring. Some of the compds. used were found to have a marked anti-HIV activity. They were also characterized by the simplicity of synthesis (2 stages) and low toxicity in vitro. Esterification of 2,3-hydroxyl radicals of the ribose ring in the nucleotide analogs was ascertained to yield compds. having immunomodulating activity. This appeared as a higher primary immune response to antigen in mice and an increased proliferative response of mononuclears to mitogens in man, and as partially inhibited tumor necrosis factor and enhanced activity of **natural killer cells**. The nucleoside analogs showed a lower immunostimulating activity than did their 5'-phosphonates. The immunomodulating capacity of nucleoside derivs. was shown to be assocd. with induction of regulatory cells. By using the modified nucleotides it might be possible to design drugs that are capable not only to suppress HIV replication, but to enhance some processes that lead to virus elimination from the body. These bifunctional compds. may be useful in developing extracorporeal approaches to the treatment of HIV infections due to the administration of intrinsic therapeutically induced cells that regulate immunogenesis.
ST nucleoside phosphonate immunostimulant HIV
IT Acquired immune deficiency syndrome
(inhibitors of, nucleoside phosphonate analogs as)
IT Immunostimulants
(nucleoside phosphonate analogs as, AIDS in relation to)
IT Nucleosides, biological studies
Nucleotides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(analogs, immunostimulant activity of, AIDS in relation to)
IT Virus, animal
(human immunodeficiency 1, inhibitors of, nucleoside phosphonate analogs as)
IT 362-42-5 **3250-02-0** 13241-21-9 **16658-10-9**
67685-73-8 68973-49-9 73452-47-8 149759-92-2 149759-93-3
149759-94-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(immunostimulant activity of, AIDS in relation to)
IT **3250-02-0 16658-10-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(immunostimulant activity of, AIDS in relation to)
RN 3250-02-0 HCAPLUS
CN Adenosine, 2',3'-O-(ethoxymethylene)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 16658-10-9 HCAPLUS
CN Adenosine, 2',3'-O-(methoxymethylene)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:247106 HCAPLUS
DN 118:247106
TI Combination treatment of 2-chlorodeoxyadenosine and type I interferon on hairy cell leukemia-like cells: cytotoxic effect and MHC-unrestricted **killer cell** regulation
AU Reiter, Zvi; Tomson, Sue; Ozes, Osman N.; Taylor, Milton W.
CS Fac. Med., Technion, Haifa, Israel
SO Blood (**1993**), 81(7), 1699-708
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Hairy cell leukemia (HCL) is a lymphoproliferative disorder of B lymphocytes. Interferons (IFNs), esp. the .alpha.-subtype, have antitumor effects in HCL patients. The purine analog 2-chlorodeoxyadenosine (2-CdA) is an effective agent in the treatment of HCL. The HCL cell lines HS-1 and HS-2 as well as Eskol and its IFN-resistant clone IREs-4 are sensitive to the cytotoxic activity of 2-CdA. Combination treatment of IFN-Con1 and 2-CdA has a synergistic inhibitory effect at low doses but an additive inhibitory effect at higher concns. IREs-4 cells respond only to 2-CdA treatment. All HCL cell lines are resistant to **natural killer (NK) cell**-mediated cytotoxicity (CMC) but are relatively sensitive to IFN-Con1-primed or interleukin-2 (IL-2)-primed NK-CMC activities. No inhibition in the killing ability is found when only the effector cells (NK) are treated with 2-CdA.

Pretreatment of the HCL target cells with 2-CdA increases their susceptibility to NK-CMC. Pretreatment with IFN-Con1 can reduce the susceptibility of target cells to NK-CMC in HS-1, HS-2, and Eskol cells but not in the IFN-resistant clone IREs-4. 2-CdA abolishes this IFN-induced protection against NK-CMC. Normal fibroblasts respond only to treatments with relatively high doses of 2-CdA, and only a moderate additive cell growth inhibitory effect are seen with combinations of 2-CdA and IFN-Con1. Only high doses of 2-CdA increase the susceptibility of fibroblast culture to NK-CMC. Thus, combinations of IFN-Con1 and 2-CdA enhance the in vitro direct antiproliferative/cytotoxic activity of each treatment alone and increase the efficacy of the NK activity against the HCL cell lines.

ST leukemia chlorodeoxyadenosine interferon antitumor synergism; lymphocyte **natural killer** antitumor chlorodeoxyadenosine interferon

IT Neoplasm inhibitors
(leukemia, chlorodeoxyadenosine plus interferon as, **natural killer cells** role in)

IT **Lymphocyte**
(**natural killer cell**, antileukemic activity of chlorodeoxyadenosine and interferon in relation to regulation of)

IT Drug interactions
(synergistic, of chlorodeoxyadenosine with interferon, in hairy-cell leukemia, **natural killer cells** role in)

IT Interferons
RL: BIOL (Biological study)
(.alpha., Con-1, antileukemic activity of chlorodeoxyadenosine and, **natural killer cells** role in)

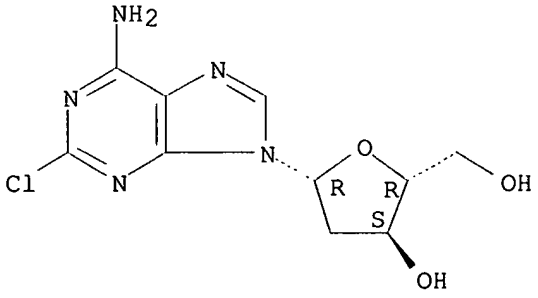
IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antileukemic activity of interferon and, **natural killer cells** role in)

IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antileukemic activity of interferon and, **natural killer cells** role in)

RN 4291-63-8 HCAPLUS

CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2002 ACS

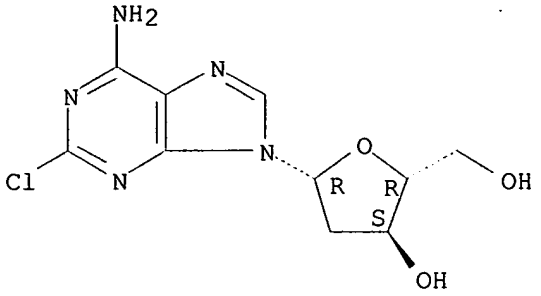
AN 1992:400415 HCAPLUS

DN 117:415

TI A dual antitumor effect of a combination of interferon-.alpha. and 5-fluorouracil or 2-chlorodeoxyadenosine on **natural killer (NK) cell** mediated cytotoxicity

AU Reiter, Zvi; Ozes, Osman N.; Tomson, Sue; Blatt, Lawrence M.; Taylor, Milton W.
CS Inst. Mol. Cell. Biol., Indiana Univ., Bloomington, IN, 47405, USA
SO Advances in Experimental Medicine and Biology (**1991**), 309A(Purine Pyrimidine Metab. Man 7, Pt. A), 69-73
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Interferon (IFN)-.alpha. is now widely used in the treatment of a no. of specific neoplasms, such as hairy cell leukemia and Kaposi's sarcoma (1,2). However the therapeutic effects of IFNs are still rather limited and the success in the treatment of other cancers has not been great. One possible approach to improving the efficiency of IFN treatment is to combine it with the use of chemotherapeutic agents, such as purine and pyrimidine analogs. Preliminary data indicates that a combination of 5-fluorouracil (5-FU) and IFN-.alpha. is clin. relevant, and this combination has been used in the treatment of colon cancer and renal carcinoma with some success. In this study, the authors examd. the effect of pre-treating both **NK cells** and target cells with the pyrimidine analog, 5-FU, and the purine analog, (2-CdA), in combination with IFN-.alpha.. This combination has additive antiproliferative effect on tumor cells, sensitized the target cells to NK cytotoxic effects and abolished the protection of target cells by IFN.
ST interferon alpha fluorouracil chlorodeoxyadenosine antitumor; **natural killer** cytotoxicity interferon fluorouracil chlorodeoxyadenosine
IT Neoplasm inhibitors
(interferon-.alpha. and fluorouracil or chlorodeoxyadensoine, **natural killer cell** mediated cytotoxicity stimulation by)
IT **Lymphocyte**
(**natural killer cell**, cytotoxicity of, interferon-.alpha. and fluorouracil or chlorodeoxyadenosine stimulation of)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha., antitumor activity of fluorouracyl and chlorodeoxyadenosine in combination with, **natural killer cell** mediated cytotoxicity stimulation by)
IT 51-21-8, 5-Fluorouracil **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BIOL (Biological study)
(antitumor effect of interferon-.alpha. and, on **natural killer cell** mediated cytotoxicity)
IT **4291-63-8**, 2-Chlorodeoxyadenosine
RL: BIOL (Biological study)
(antitumor effect of interferon-.alpha. and, on **natural killer cell** mediated cytotoxicity)
RN 4291-63-8 HCAPLUS
CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



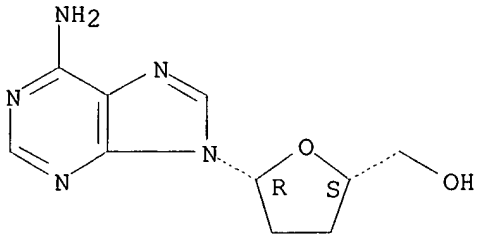
L96 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:67168 HCAPLUS
DN 116:67168
TI Plant extracts for decreasing side effects of antiviral drugs and increasing the immune function
IN Liu, Yaguang
PA USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-70
ICS A61K031-765
NCL 514025000
CC 63-4 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5071839	A	19911210	US 1987-115872	19871102 <--

AB A compn. for preventing side effects of virucides and increasing the immune functions is composed of 2 ingredients: (1) polysaccharide of Wang Qi derived from a plant, Astragalus membranaceus Bge and A. chrysopterus Bge and ginsenoside derived from Panax quinquefolium and P. ginseng. A mixt. contg. polysaccharides of Wang Qi 20-80 and ginsenoside 20-80 % can be formulated into tablets, capsules, or syrups by conventional methods. Thus, an ethanol ext. of ginseng powder was worked up to give a ginsenoside and a water ext. of Astragalus for the polysaccharide. A mixt. contg. ginsenoside and the polysaccharide was coadministered to mice with a virucide (5'-azacytidine, 2',3'-dideoxyadenoside, cyclophosphamide, cytarabine, and ribavirin, resp.) and the effects on **natural killer cells**, bone-marrow cells, lymphoblastoid transformation, rosette formation, and phagocytosis of peritoneal macrophage were obsd.
ST ginsenoside polysaccharide Astragalus immunostimulant; virucide side effect ginsenoside Astragalus polysaccharide
IT Pharmaceutical natural products
RL: BIOL (Biological study)
(Wang Qi, side effects from virucides prevention by ginsenoside and)
IT Polysaccharides, biological studies
RL: BIOL (Biological study)
(from Astragalus, side effects of virucides prevention by ginsenoside and)
IT Immunostimulants
(ginsenosides and Astragalus polysaccharides combinations)
IT Astragalus chrysopterus
Astragalus membranaceus
(polysaccharides from, side effects of virucides prevention by

ginsenoside and)
IT Virucides and Virustats
(side effect of, prevention of, ginsenoside and polysaccharides from Astragalus for)
IT Glycosides
RL: BIOL (Biological study)
(ginsenosides, side effects from virucides prevention by polysaccharides from Astragalus and)
IT Ginseng
(P. pseudoginseng, ginsenoside from, side effects of virucides prevention by Astragalus polysaccharides and)
IT Ginseng
(P. quinquefolium, ginsenoside from, side effects of virucides prevention by Astragalus polysaccharides and)
IT 50-18-0, Cyclophosphamide 147-94-4, Cytarabine 320-67-2
4097-22-7 36791-04-5, Ribavirin
RL: PRP (Properties)
(side effect of, prevention of, ginsenoside and polysaccharides from Astragalus for)
IT **4097-22-7**
RL: PRP (Properties)
(side effect of, prevention of, ginsenoside and polysaccharides from Astragalus for)
RN 4097-22-7 HCAPLUS
CN Adenosine, 2',3'-dideoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L96 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:545035 HCAPLUS
DN 113:145035
TI **Adenosine receptors** and modulation of **natural killer cell** activity by **purine** nucleosides
AU Priebe, Teresa; Platsoucas, Chris D.; Nelson, J. Arly
CS M. D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SO Cancer Research (**1990**), 50(14), 4328-31
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
CC 1-7 (Pharmacology)
AB **Natural killer (NK) cell** activity is inhibited in vivo by the **adenosine** analog tubercidin (Tub) and stimulated by the deoxyadenosine analog 2-fluoro-1-.beta.-D-arabinofuranosyladenine 5'-monophosphate (F-ara-AMP) in the spleen lymphocytes from mice. The inhibition by Tub and stimulation by F-ara-AMP of **NK cell** activity are readily demonstrable in murine and human lymphocytes exposed to the drugs in vitro. In mouse spleen lymphocytes, **NK cell** activity is also inhibited by **adenosine receptor** A2 agonists, whereas potent A1 **receptor** agonists are more effective stimulators. Inhibition produced by **adenosine**, deoxyadenosine, and **adenosine**

receptor agonists, but not by Tub, is partially prevented by the **adenosine receptor** antagonist 1,3-dipropyl-8-phenylxanthine amine congener. Agents that stimulate **NK cell** activity (deoxyadenosine, A1 **receptor** agonists, F-ara-AMP) do not increase further the 1.5-fold enhancement produced by a 10-6M 1,3-dipropyl-8-phenylxanthine amine congener. The nucleoside transport inhibitor p-nitrobenzylthioinosine 5'-monophosphate has no effect on **NK cell** activity or intracellular ribonucleotide pools; however, it partially prevents Tub 5'-triphosphate formation, ATP depletion, and **NK cell** inhibition in mouse spleen cells treated with Tub. Nitrobenzylthioinosine 5'-monophosphate also partially prevents the F-ara-AMP stimulation of **NK cell** activity, but it does not influence the effects of **adenosine** or deoxyadenosine. The results obtained with the **adenosine receptor** agonists suggest roles for both A1 and A2 **receptors** in regulating murine **NK cell** activity. Tub inhibition of **NK cell** activity does not involve **adenosine receptors**; however, inhibition by the other agents may be mediated via an A2 **receptor** (stimulatory for adenylyl cyclase). Since p-nitrobenzylthioinosine 5'-monophosphate inhibited the stimulation of **NK cell** activity by F-ara-AMP, this stimulation may occur via an intracellular P site (inhibitory to adenylyl cyclase).

ST killer lymphocyte **adenosine receptor purine** nucleoside; splenocyte killer **adenosine receptor purine** nucleoside

IT **Lymphocyte**
(**natural killer**, of spleen, adenine nucleosides effects on, **adenosine receptors** mediation of)

IT **Receptors**
RL: BIOL (Biological study)
(**purinergic** A1, splenocyte **natural killer** activity response to adenine nucleosides mediation by)

IT **Receptors**
RL: BIOL (Biological study)
(**purinergic** A2, splenocyte **natural killer** activity response to adenine nucleosides mediation by)

IT Spleen
(splenocyte, **natural killer** activity of, adenine nucleosides effect on, **adenosine receptors** mediation of)

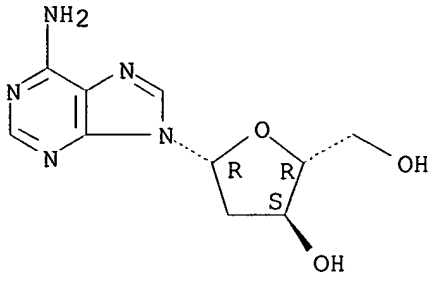
IT 58-61-7, **Adenosine**, biological studies 69-33-0, Tubercidin 73-24-5D, Adenine, nucleotides **958-09-8**, Deoxyadenosine 35920-39-9, 5'-N-Ethylcarboxamidoadenosine 38594-97-7 41552-82-3, N6-Cyclopentyladenosine **53296-10-9**, 2-Phenylaminoadenosine 65199-10-2 96865-92-8 129576-22-3
RL: BIOL (Biological study)
(splenocyte **natural killer** activity modulation by, **adenosine receptors** in)

IT **958-09-8**, Deoxyadenosine **53296-10-9**, 2-Phenylaminoadenosine
RL: BIOL (Biological study)
(splenocyte **natural killer** activity modulation by, **adenosine receptors** in)

RN 958-09-8 HCAPLUS

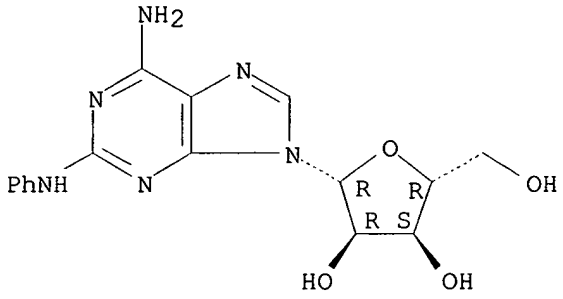
CN Adenosine, 2'-deoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 53296-10-9 HCAPLUS
CN Adenosine, 2-(phenylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L96 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:568710 HCAPLUS
DN 109:168710
TI Selective modulation of antibody response and **natural killer cell** activity by purine nucleoside analogs
AU Priebe, Teresa; Kandil, Osama; Nakic, Melita; Pan, Bih Fang; Nelson, J. Arly
CS M. D. Anderson Hosp. Tumor Inst., Univ. Texas, Houston, TX, 77030, USA
SO Cancer Res. (**1988**), 48(17), 4799-803
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB Analogs that are poor substrates for adenosine deaminase or purine nucleoside phosphorylase may mimic immunodeficiencies assocd. with the enzyme deficiencies, and their activities may be directed toward selected lymphocyte subpopulations. Four analogs were studied for their effects on primary antibody response to either a T-dependent (sheep erythrocytes) or T-independent (trinitrophenyl-conjugated Escherichia coli lipopolysaccharide) antigen as well as effects on T-cytotoxic and **natural killer cell** activities in mice. The nucleosides were: an adenosine analog, tubercidin; two deoxyadenosine analogs, 2-chloro-2'-deoxyadenosine and 2-fluoroadenine arabinoside-5'-phosphate; and a deoxyguanosine analog, 9-.beta.-D-arabinosylguanine. Drugs were given i.p. once daily for 3 consecutive days. Immune responses were detd. in spleen cell suspensions 1 day after the last dose. Tubercidin inhibited both T-cytotoxic and **natural killer cell** activities at doses that did not reduce primary antibody response, whereas the reverse was true for 2-chloro-2'-deoxyadenosine and 2-fluoroadenine arabinoside-5'-phosphate. At higher doses, T-cytotoxic lymphocytes appeared to be more sensitive

than **natural killer cells** to the deoxyadenosine analogs. 9-.beta.-D-Arabinosylguanine did not selectively inhibit the immune responses at doses that clearly reduced the yield of spleen lymphocytes. Assuming the analogs mimic endogenous nucleosides, the results suggest that **natural killer cells** are more sensitive to adenosine than are those cells responsible for primary antibody response, whereas the reverse is true for deoxyadenosine.

ST purine nucleoside analog antibody lymphocyte immunodeficiency

IT Immunodeficiency
(from purine nucleoside analogs, antibody response and **natural killer cell** activity in relation to)

IT **Lymphocyte**
(**T-, cytotoxic**, purine nucleoside analogs toxicity to, antibody response in relation to)

IT Immunosuppression
(cellular, from purine nucleoside analogs, humoral immunosuppression in relation to)

IT Immunosuppression
(humoral, by purine nucleoside analogs, **natural killer cell** activity in relation to)

IT **Lymphocyte**
(**natural killer**, purine nucleoside analogs toxicity to, antibody response in relation to)

IT Nucleosides, biological studies
RL: BIOL (Biological study)
(purine, antibody response and **natural killer cell** activity modulation by)

IT 69-33-0, Tubercidin **4291-63-8**, 2-Chloro, 2'-deoxyadenosine
38819-10-2 75607-67-9
RL: BIOL (Biological study)
(antibody response and **natural killer cell** activity modulation by)

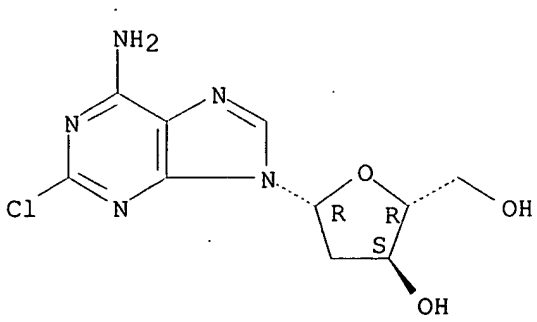
IT 58-61-7, biological studies **958-09-8**
RL: PRP (Properties)
(toxicity of, to antibody-forming vs. **natural killer** lymphocytes)

IT **4291-63-8**, 2-Chloro, 2'-deoxyadenosine
RL: BIOL (Biological study)
(antibody response and **natural killer cell** activity modulation by)

RN 4291-63-8 HCAPLUS

CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.

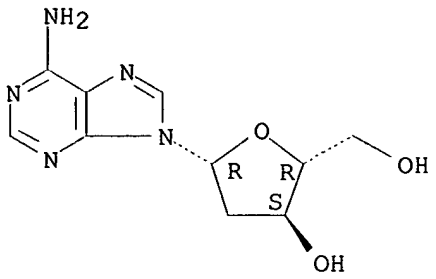


IT **958-09-8**
RL: PRP (Properties)
(toxicity of, to antibody-forming vs. **natural killer** lymphocytes)

RN 958-09-8 HCAPLUS

CN Adenosine, 2'-deoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

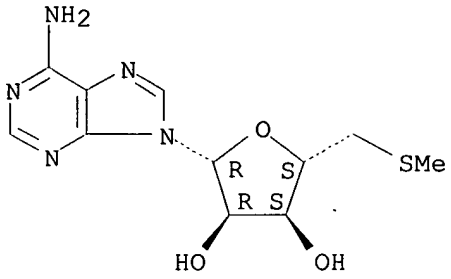
Absolute stereochemistry.



L96 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1985:72539 HCAPLUS
DN 102:72539
TI Effect of 5'-methylthioadenosine, 3-deazaadenosine, and related compounds on human **natural killer cell** activity. Relation to cyclic AMP and methylation potential
AU Fredholm, B. B.; Jondal, M.; Lanefelt, F.; Ng, J.
CS Dep. Pharmacol., Karolinska Inst., Stockholm, 104 01, Swed.
SO Scand. J. Immunol. (**1984**), 20(6), 511-18
CODEN: SJIMAX; ISSN: 0300-9475
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 15
AB The effect of 5'-methylthioadenosine (MTA) [**2457-80-9**] on human lymphocyte **natural killer** (**NK**) **cell** activity was examd. and compared with the effect of 3-deazaadenosine (c3-ado) [6736-58-9] and periodate-oxidized adenosine (ado-ox) [29847-35-6]. MTA inhibited **NK cell** activity in concns. >30 .mu.M, but in concns. <10 .mu.M, a slight enhancing effect was often obsd. C3-ado and ado-ox were 10 and 3 times more potent, resp. as inhibitory agents and did not increase **NK cell** activity in low concns. The inhibitory effect of c3-ado was unaffected by preincubation of the cells but was enhanced by the addn. of L-homocysteine. In concns. that caused inhibition of **NK cell** activity, all 3 agents caused a fall in the methylation index (AdoMet/AdoHcy) but no or an inconsistent effect on the level of cyclic AMP [60-92-4]. An increase in the level of AdoHcy was obsd. already after 1 h of incubation, but was more pronounced after 4 h of preincubation with the adenosine derivs. The inhibition of cytotoxicity was mainly on their initiation of lysis, with a smaller effect on target cell binding. Antibody-dependent cellular cytotoxicity and lectin-dependent cellular cytotoxicity appeared to be less sensitive to inhibition by c3-ado. Thus, several adenosine analogs inhibit **NK -cell**-mediated cytotoxicity in parallel with a decreased methylation index. Apparently, a methylation step is crit. in lymphocyte-mediated cytotoxicity and **NK cell** activity is more sensitive to inhibition of this step than antibody- or lectin-dependent cytotoxicity.
ST **natural killer** lymphocyte adenosine analog; methylthioadenosine **natural killer** lymphocyte; cAMP **natural killer** lymphocyte methylthioadenosine
IT **Lymphocyte**
(**natural killer**, adenosine analogs. effect on human, cyclic AMP and methylation potential in relation to)
IT 58-61-7D, analogs **2457-80-9** 6736-58-9 29847-35-6

RL: BIOL (Biological study)
(**natural killer** lymphocyte activity response to, of human, cAMP and methylation potential in relation to)
IT 60-92-4
RL: BIOL (Biological study)
(of **natural killer** lymphocytes of humans, adenosine analogs effect on)
IT **2457-80-9**
RL: BIOL (Biological study)
(**natural killer** lymphocyte activity response to, of human, cAMP and methylation potential in relation to)
RN 2457-80-9 HCAPLUS
CN Adenosine, 5'-S-methyl-5'-thio- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

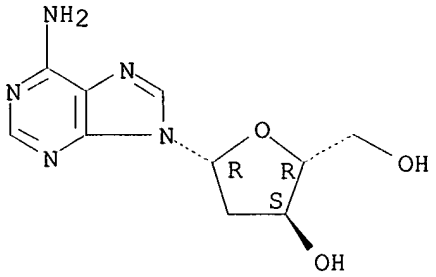
Absolute stereochemistry.



L96 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2002 ACS
AN 1983:32907 HCAPLUS
DN 98:32907
TI Inhibition of K and NK lymphocyte cytotoxicity by an inhibitor of adenosine deaminase and deoxyadenosine
AU Grever, Michael R.; Siaw, Martin F. E.; Coleman, Mary Sue; Whisler, Ronald L.; Balcerzak, Stanley P.
CS Dep. Med., Ohio State Univ., Columbus, OH, USA
SO J. Immunol. (**1983**), 130(1), 365-9
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-10 (Immunochemistry)
AB The effect of inhibition of adenosine deaminase by 2'deoxycoformycin (dCF) on human lymphocyte antibody-dependent cytotoxicity (ADCC) and nonantibody-dependent cytotoxicity (non-ADCC) was investigated. Human lymphocytes were incubated in vitro for 72 h under the following conditions in complete RPMI and 10% fetal calf serum: a) medium alone; b) supplemented with dCF 10-6M; c) supplemented with 2'deoxyadenosine (dAdo), 10-6M; and d) supplemented with both dCF and dAdo. After incubation, the lymphocytes were thoroughly washed and were resuspended in fresh medium before use in the cytotoxicity assays. Lymphocytes exposed to the combination of dCF and dAdo have marked impairment (50%) in both ADCC and non-ADCC. These functional impairments in both **Killer** and **natural killer** (K and **NK**) **cell** activity did not represent diminished cell viability or decreased frequency of binding of the lymphocytes to the target cells. Substantive changes in the intracellular nucleotide pools were not obsd. These data suggest an immunosuppressive effect may be achievable in vivo with low doses of dCF that do not cause massive alteration of the intracellular nucleotide pools.
ST immunosuppression deoxycoformycin; adenosine deaminase lymphocyte cytotoxicity
IT **Lymphocyte**

Lymphocyte
(**natural killer**, cytotoxicity of, inhibition of, by adenosine deaminase and deoxyadenosine inhibitor)
IT **958-09-8** 9026-93-1
RL: BIOL (Biological study)
(inhibitor of, **natural killer** and **killer** lymphocyte cytotoxicity inhibition by)
IT 53910-25-1
RL: BIOL (Biological study)
(**natural killer** and **killer** lymphocytes cytotoxicity inhibition by)
IT **958-09-8**
RL: BIOL (Biological study)
(inhibitor of, **natural killer** and **killer** lymphocyte cytotoxicity inhibition by)
RN 958-09-8 HCAPLUS
CN Adenosine, 2'-deoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> fil reg
FILE 'REGISTRY' ENTERED AT 17:02:34 ON 21 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 20 OCT 2002 HIGHEST RN 463296-69-7
DICTIONARY FILE UPDATES: 20 OCT 2002 HIGHEST RN 463296-69-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

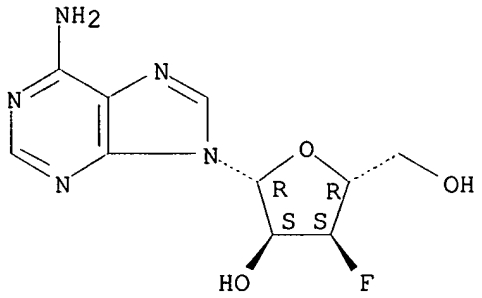
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can tot l94

L94 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **75059-22-2** REGISTRY

CN Adenosine, 3'-deoxy-3'-fluoro- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3'-Deoxy-3'-fluoroadenosine
FS STEREOSEARCH
MF C10 H12 F N5 O3
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CASREACT, CHEMINFORMRX, CIN, MEDLINE, PROMT, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

30 REFERENCES IN FILE CA (1962 TO DATE)
30 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:340939

REFERENCE 2: 132:77394

REFERENCE 3: 128:294991

REFERENCE 4: 128:244274

REFERENCE 5: 124:9259

REFERENCE 6: 123:257240

REFERENCE 7: 122:291411

REFERENCE 8: 120:289467

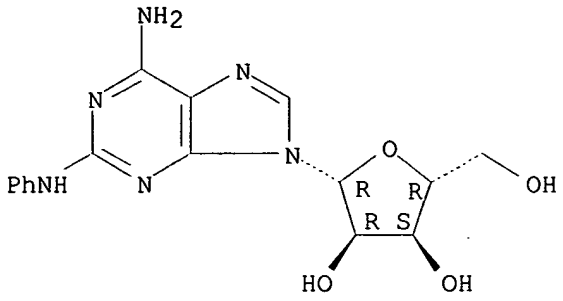
REFERENCE 9: 118:7311

REFERENCE 10: 116:214849

L94 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **53296-10-9** REGISTRY
CN Adenosine, 2-(phenylamino)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Phenylaminoadenosine
CN CV 1808
FS STEREOSEARCH
MF **C16 H18 N6 O4**
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, DDFU, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

111 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
111 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:28514

REFERENCE 2: 135:335153

REFERENCE 3: 135:162508

REFERENCE 4: 133:182707

REFERENCE 5: 133:115443

REFERENCE 6: 130:177447

REFERENCE 7: 130:90521

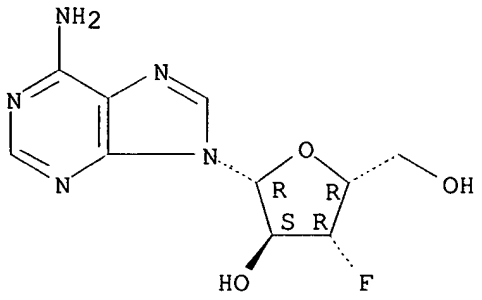
REFERENCE 8: 130:90482

REFERENCE 9: 130:29255

REFERENCE 10: 129:145069

L94 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **20535-16-4** REGISTRY
CN 9H-Purin-6-amine, 9-(3-deoxy-3-fluoro-.beta.-D-xylofuranosyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenine, 9-(3-deoxy-3-fluoro-.beta.-D-xylofuranosyl)- (8CI)
OTHER NAMES:
CN 9-(3-Deoxy-3-fluoro-.beta.-D-xylofuranosyl)adenine
FS STEREOSEARCH
DR 25150-20-3
MF C10 H12 F N5 O3
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, MEDLINE, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16 REFERENCES IN FILE CA (1962 TO DATE)
16 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 132:77394

REFERENCE 2: 129:175222

REFERENCE 3: 127:34447

REFERENCE 4: 124:30239

REFERENCE 5: 123:257240

REFERENCE 6: 120:289467

REFERENCE 7: 114:143890

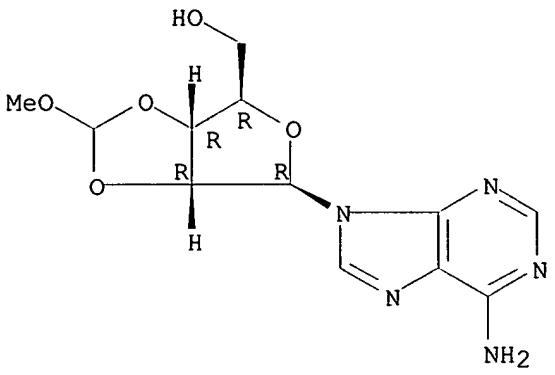
REFERENCE 8: 111:233479

REFERENCE 9: 111:58281

REFERENCE 10: 110:71643

L94 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **16658-10-9** REGISTRY
CN Adenosine, 2',3'-O-(methoxymethylene)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenosine, cyclic 2',3'-(methyl orthoformate) (7CI, 8CI)
CN Furo[3,4-d]-1,3-dioxole, adenosine deriv.
FS STEREOSEARCH
MF **C12 H15 N5 O5**
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1962 TO DATE)
8 REFERENCES IN FILE CAPLUS (1962 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 121:134648

REFERENCE 2: 120:218379

REFERENCE 3: 119:131115

REFERENCE 4: 100:156923

REFERENCE 5: 97:6718

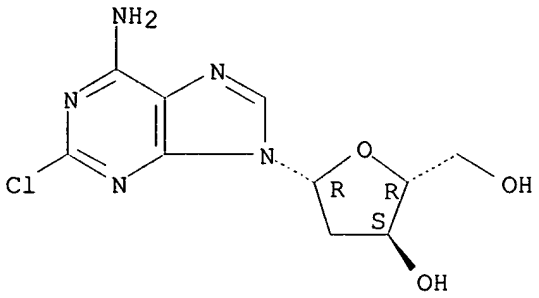
REFERENCE 6: 92:17867

REFERENCE 7: 92:1735

REFERENCE 8: 67:3211

L94 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **4291-63-8** REGISTRY
CN Adenosine, 2-chloro-2'-deoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-CdA
CN 2-Chloro-2'-deoxy-.beta.-adenosine
CN 2-Chloro-2'-deoxyadenosine
CN 2-Chloro-6-amino-9-(2-deoxy-.beta.-D-erythro-pentofuranosyl)purine
CN 2-Chlorodeoxyadenosine
CN Cladarabine
CN Cladribine
CN Leustatin
CN NSC 105014-F
CN RWJ 26251
FS STEREOSEARCH
DR 24757-90-2
MF C10 H12 Cl N5 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

574 REFERENCES IN FILE CA (1962 TO DATE)
9 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
576 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:252841

REFERENCE 2: 137:241829

REFERENCE 3: 137:231369

REFERENCE 4: 137:228688

REFERENCE 5: 137:226339

REFERENCE 6: 137:226114

REFERENCE 7: 137:210933

REFERENCE 8: 137:210932

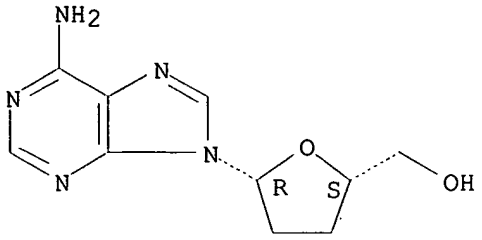
REFERENCE 9: 137:210579

REFERENCE 10: 137:210331

L94 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **4097-22-7** REGISTRY
CN Adenosine, 2',3'-dideoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .beta.-D-erythro-Pentofuranoside, adenine-9 2,3-dideoxy-
CN 2',3'-Dideoxyadenosine
CN Dideoxyadenosine
CN NSC 98700
FS STEREOSEARCH
DR 6699-71-4, 117174-26-2
MF C10 H13 N5 O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

417 REFERENCES IN FILE CA (1962 TO DATE)
25 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
417 REFERENCES IN FILE CAPLUS (1962 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:232453

REFERENCE 2: 137:137271

REFERENCE 3: 137:136024

REFERENCE 4: 137:43682

REFERENCE 5: 137:15298

REFERENCE 6: 136:340939

REFERENCE 7: 136:305088

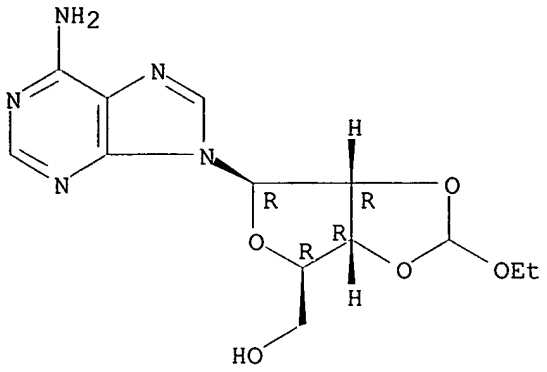
REFERENCE 8: 136:226405

REFERENCE 9: 136:144720

REFERENCE 10: 136:74772

L94 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **3250-02-0** REGISTRY
CN Adenosine, 2',3'-O-(ethoxymethylene)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenosine, cyclic 2',3'-(ethyl orthoformate) (7CI, 8CI)
CN Furo[3,4-d]-1,3-dioxole, adenosine deriv.
OTHER NAMES:
CN 2':3'-O-Ethoxymethylene adenosine
FS STEREOSEARCH
MF **C13 H17 N5 O5**
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29 REFERENCES IN FILE CA (1962 TO DATE)
29 REFERENCES IN FILE CAPLUS (1962 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:232846

REFERENCE 2: 137:232844

REFERENCE 3: 127:95521

REFERENCE 4: 122:106395

REFERENCE 5: 119:131115

REFERENCE 6: 114:247644

REFERENCE 7: 114:159626

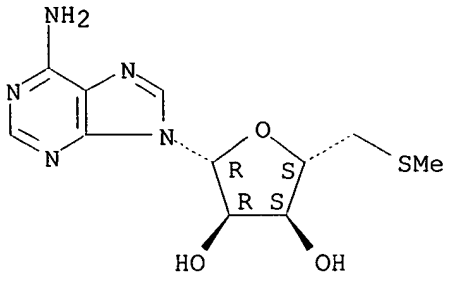
REFERENCE 8: 114:122934

REFERENCE 9: 114:43455

REFERENCE 10: 112:179711

L94 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **2457-80-9** REGISTRY
CN Adenosine, 5'-S-methyl-5'-thio- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .beta.-D-Ribofuranose, 1-(6-amino-9H-purin-9-yl)-1-deoxy-5-S-methyl-5-thio-
CN 5'-(Methylthio)-5'-deoxyadenosine
CN 5'-(Methylthio)adenosine
CN 5'-Deoxy(methylthio)adenosine
CN 5'-Deoxy-5'-(methylthio)adenosine
CN 5'-S-Methyl-5'-thioadenosine
CN 5'-S-Methylthioadenosine
CN Vitamin L2
FS STEREOSEARCH
DR 37311-40-3
MF C11 H15 N5 O3 S
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CSCHEM, DDFU, DRUGU, EMBASE, MEDLINE, NAPRALERT, NIOSHTIC, PROMT, RTECS*, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

441 REFERENCES IN FILE CA (1962 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
441 REFERENCES IN FILE CAPLUS (1962 TO DATE)
20 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:195570

REFERENCE 2: 137:135077

REFERENCE 3: 137:121265

REFERENCE 4: 137:90317

REFERENCE 5: 137:60031

REFERENCE 6: 137:2882

REFERENCE 7: 136:383433

REFERENCE 8: 136:275806

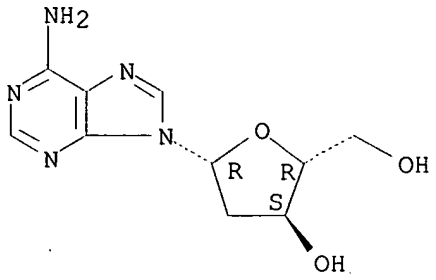
REFERENCE 9: 136:228645

REFERENCE 10: 136:196681

L94 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2002 ACS
RN **958-09-8** REGISTRY
CN Adenosine, 2'-deoxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .beta.-D-erythro-Pentofuranoside, adenine-9 2-deoxy-
CN .beta.-D-Ribofuranose, 1-(6-amino-9H-purin-9-yl)-1,2-dideoxy-
CN 2'-Deoxyadenosine
CN 9-(2-Deoxy-.beta.-D-erythro-pentofuranosyl)adenine
CN 9H-Purin-6-amine, 9-(2-deoxy-.beta.-D-erythro-pentofuranosyl)-
CN 9H-Purin-6-amine, 9-(2-deoxy-.beta.-D-ribofuranosyl)-
CN Adenine deoxyribonucleoside
CN Adenine deoxyribose
CN Adenyldeoxyriboside
CN dA
CN Deoxyadenosine
CN Desoxyadenosine
FS STEREOSEARCH
DR 7005-15-4

MF C10 H13 N5 O3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, NIOSHTIC, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2587 REFERENCES IN FILE CA (1962 TO DATE)
131 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2589 REFERENCES IN FILE CAPLUS (1962 TO DATE)
38 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 137:252841

REFERENCE 2: 137:247887

REFERENCE 3: 137:243083

REFERENCE 4: 137:196642

REFERENCE 5: 137:191209

REFERENCE 6: 137:185768

REFERENCE 7: 137:185752

REFERENCE 8: 137:136468

REFERENCE 9: 137:93957

REFERENCE 10: 137:93954

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

=> fil medline
FILE 'MEDLINE' ENTERED AT 13:04:04 ON 21 OCT 2002

FILE LAST UPDATED: 19 OCT 2002 (20021019/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d all tot

L40 ANSWER 1 OF 19 MEDLINE
AN 2002297101 MEDLINE
DN 22033731 PubMed ID: 12037688
TI Evidence for involvement of Wnt signaling pathway in **IB-MECA** mediated suppression of melanoma cells.
AU Fishman Pnina; Madi Lea; Bar-Yehuda Sara; Barer Faina; Del Valle Luis; Khalili Kamel
CS Laboratory of Clinical and Tumor Immunology, The Felsenstein Medical Research Center, Tel Aviv University, Sackler Faculty of Medicine, Rabin Medical Center, Petach-Tikva 49100, Israel.. pfishman@post.tau.ac.il
SO ONCOGENE, (2002 Jun 6) 21 (25) 4060-4.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020531
Last Updated on STN: 20020623
Entered Medline: 20020621
AB The **A3 adenosine receptor, A3AR,** belongs to the family of Gi proteins, which upon induction, suppresses the formation of cAMP and its downstream effectors. Recent studies have indicated that activation of **A3AR** by its agonist, **IB-MECA**, results in growth inhibition of malignant cells. Here we demonstrate the ability of **IB-MECA** to decrease the levels of protein kinase A, a downstream effector of cAMP, and protein kinase B/Akt in melanoma cells. Examination of glycogen synthase kinase 3beta, GSK-3beta, whose phosphorylation is controlled by protein kinase A and B, showed a substantial decrease in the levels of its phosphorylated form and an increase in total GSK-3beta levels in **IB-MECA** treated melanoma cells. This observation suggests that the treatment of cells with **IB-MECA** augments the activity of GSK-3beta in the cells. Evaluation of beta-catenin, a key component of Wnt signaling pathway which, upon phosphorylation by GSK-3beta rapidly ubiquitinates, showed a substantial decrease in its level after **IB-MECA** treatment. Accordingly, the level of beta-catenin responsive cell growth regulatory genes including c-myc and cyclin D1 was severely declined upon treatment of the cells with **IB-MECA**. These observations which link cAMP to the Wnt signaling pathway provide mechanistic evidence for the involvement of Wnt pathway via its key elements GSK-3beta and beta-catenin in the anti-tumor activity of **A3AR** agonists.
CT Check Tags: Human
*Adenosine: AA, analogs & derivatives
*Adenosine: PD, pharmacology
Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
*Cell Division: DE, drug effects

Cell Division: PH, physiology
Cyclic AMP: ME, metabolism
Cyclic AMP-Dependent Protein Kinases: ME, metabolism
Cyclins: ME, metabolism
Cytoskeletal Proteins: ME, metabolism
Down-Regulation
Melanoma: DT, drug therapy
Melanoma: EN, enzymology
***Melanoma: ME, metabolism**
*Proto-Oncogene Proteins: ME, metabolism
***Receptors, Purinergic P1: AG, agonists**
*Signal Transduction: PH, physiology
***Tumor Cells, Cultured: DE, drug effects**
Ubiquitin

RN 146409-33-8 (beta catenin); **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; 58-61-7 (Adenosine); 60-92-4 (Cyclic AMP)

CN 0 (Cyclins); 0 (Cytoskeletal Proteins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Purinergic P1); 0 (Ubiquitin); 0 (proto-oncogene protein akt); 0 (proto-oncogene protein int-1); EC 2.7.1.- (myelin basic protein kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.10.- (Cyclic AMP-Dependent Protein Kinases)

L40 ANSWER 2 OF 19 MEDLINE
AN 2002290824 MEDLINE
DN 22021432 PubMed ID: 11992407
TI **Adenosine** acts through an **A3 receptor** to prevent the induction of murine anti-CD3-activated killer T cells.
AU Hoskin David W; Butler Jared J; Drapeau Dennis; Haeryfar S M Mansour; Blay Jonathan
CS Department of Microbiology and Immunology, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.. dwhoskin@is.dal.ca
SO INTERNATIONAL JOURNAL OF CANCER, (2002 May 20) 99 (3) 386-95. Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020529
Last Updated on STN: 20020620
Entered Medline: 20020619
AB **Adenosine**, a purine nucleoside found at high levels in solid tumors, is able to suppress the recognition/adhesion and effector phases of killer lymphocyte-mediated tumor cell destruction. Here, we demonstrate that **adenosine**, at concentrations that are typically present in the extracellular fluid of solid tumors, exerts a profound inhibitory effect on the induction of mouse cytotoxic T cells, without substantially affecting T-cell viability. T-cell proliferation in response to mitogenic anti-CD3 antibody was impaired in the presence of 10 microM **adenosine** (plus coformycin to inhibit endogenous **adenosine** deaminase). Antigen-specific T-cell proliferation was similarly inhibited by **adenosine**. Anti-CD3-activated killer T (AK-T) cells induced in the presence of **adenosine** exhibited reduced major histocompatibility complex-unrestricted cytotoxicity against P815 mastocytoma cells in JAM and (51)Cr-release assays. Diminished tumoricidal activity correlated with reduced expression of mRNAs coding for granzyme B, perforin, Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), as well as with diminished Nalpha-CBZ-L-lysine thiobenzylester (BLT) esterase activity. Interleukin-2 and interferon-gamma synthesis by AK-T cells was also inhibited by **adenosine**. AK-T cells express mRNA coding for A(2A), A(2B) and A(3) **receptors**, but little or no mRNA coding for A(1)

receptors. The inhibitory effect of **adenosine** on AK-T cell proliferation was blocked by an A(3) **receptor** antagonist (MRS1191) but not by an A(2) **receptor** antagonist (3,7-dimethyl-1-propargylxanthine [DMPX]). The A(3) **receptor** agonists (**N(6)-2-(4-aminophenyl)ethyladenosine** [**APNEA**] and N(6)-benzyl-5'-N-ethylcarboxamidoadenosine [N(6)-benzyl-NECA]) also inhibited AK-T cell proliferation. **Adenosine**, therefore, acts through an A(3) **receptor** to prevent AK-T cell induction. Tumor-associated **adenosine** may act through the same mechanism to impair the development of tumor-reactive T cells in cancer patients.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*Adenosine: ME, metabolism
Adenosine: PD, pharmacology
Adenosine Deaminase: ME, metabolism
*Antigens, CD3: BI, biosynthesis
Brain: ME, metabolism
Cell Division
Cell Survival
Cells, Cultured
Chromium Radioisotopes: PD, pharmacology
Dose-Response Relationship, Drug
Enzyme-Linked Immunosorbent Assay
Flow Cytometry
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
***Killer Cells: ME, metabolism**
Lymphocytes: ME, metabolism
Membrane Glycoproteins: ME, metabolism
Mice
Mice, Inbred C57BL
Mitochondria: ME, metabolism
RNA, Messenger: ME, metabolism
Receptors, Purinergic P1: AI, antagonists & inhibitors
***Receptors, Purinergic P1: ME, metabolism**
Reverse Transcriptase Polymerase Chain Reaction
T-Lymphocytes: ME, metabolism
Tetrazolium Salts: PD, pharmacology
*Theobromine: AA, analogs & derivatives
Theobromine: PD, pharmacology
Thiazoles: PD, pharmacology
Thymidine: ME, metabolism
Tumor Cells, Cultured
Tumor Necrosis Factor: ME, metabolism

RN 14114-46-6 (3,7-dimethyl-1-propargylxanthine); 298-93-1 (thiazolyl blue); 50-89-5 (Thymidine); 58-61-7 (Adenosine); 82115-62-6 (Interferon Type II); 83-67-0 (Theobromine)

CN 0 (Antigens, CD3); 0 (Chromium Radioisotopes); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1); 0 (TNF-related apoptosis-inducing ligand); 0 (Tetrazolium Salts); 0 (Thiazoles); 0 (Tumor Necrosis Factor); 0 (**adenosine A3 receptor**); EC 3.5.4.4 (Adenosine Deaminase)

L40 ANSWER 3 OF 19 MEDLINE
AN 2002239344 MEDLINE
DN 21909211 PubMed ID: 11911839
TI p53-Independent induction of Fas and apoptosis in leukemic cells by an adenosine derivative, **Cl-IB-MECA**.
AU Kim Seong Gon; Ravi Gnana; Hoffmann Carsten; Jung Yun Jin; Kim Min; Chen Aishe; Jacobson Kenneth A
CS Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National

Institutes of Health, Bethesda, MD 20892, USA.
SO BIOCHEMICAL PHARMACOLOGY, (2002 Mar 1) 63 (5) 871-80.
Journal code: 0101032. ISSN: 0006-2952.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020430
Last Updated on STN: 20020508
Entered Medline: 20020507

AB A(3) **adenosine receptor** (A(3)AR) agonists have been reported to influence cell death and survival. The effects of an A(3)AR agonist, 1-[2-chloro-6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl-beta-D-ribofuranonamide (**Cl-IB-MECA**), on apoptosis in two human leukemia cell lines, HL-60 and MOLT-4, were investigated. **Cl-IB-MECA** (> or =30 microM) increased the apoptotic fractions, as determined using fluorescence-activated cell sorting (FACS) analysis, and activated caspase 3 and poly-ADP-ribose-polymerase. Known messengers coupled to A(3)AR (phospholipase C and intracellular calcium) did not seem to play a role in the induction of apoptosis. Neither dantrolene nor BAPTA-AM affected the **Cl-IB-MECA**-induced apoptosis. **Cl-IB-MECA** failed to activate phospholipase C in HL-60 cells, while UTP activated it through endogenous P2Y(2) **receptors**. Induction of apoptosis during a 48hr exposure to **Cl-IB-MECA** was not prevented by the A(3)AR antagonists [5-propyl-2-ethyl-4-propyl-3-(ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate] (MRS 1220) or N-[9-chloro-2-(2-furanyl)[1,2,4]triazolo[1,5-c]quinazolin-5-yl]benzeneacetamide (MRS 1523). Furthermore, higher concentrations of MRS 1220, which would also antagonize A(1) and A(2A) **receptors**, were ineffective in preventing the apoptosis. Although **Cl-IB-MECA** has been shown in other systems to cause apoptosis through an A(3)AR-mediated mechanism, in these cells it appeared to be an **adenosine receptor**-independent effect, which required prolonged incubation. In both HL-60 and MOLT-4 cells, **Cl-IB-MECA** induced the expression of Fas, a death **receptor**. This induction of Fas was not dependent upon p53, because p53 is not expressed in an active form in either HL-60 or MOLT-4 cells. **Cl-IB-MECA**-induced apoptosis in HL-60 cells was augmented by an agonistic Fas antibody, CH-11, and this increase was suppressed by the antagonistic anti-Fas antibody ZB-4. Therefore, **Cl-IB-MECA** induced apoptosis via a novel, p53-independent up-regulation of Fas.

CT Check Tags: Human
*Adenosine: AA, analogs & derivatives
*Adenosine: PD, pharmacology
Antibodies: PD, pharmacology
*Antigens, CD95: BI, biosynthesis
Antigens, CD95: IM, immunology
*Apoptosis
Blotting, Western
Calcium: ME, metabolism
Drug Interactions
HL-60 Cells
Leukemia: PA, pathology
*Phospholipase C: ME, metabolism
*Protein p53: ME, metabolism
Receptors, Purinergic P1: AI, antagonists & inhibitors
Tumor Cells, Cultured
RN 58-61-7 (Adenosine); 7440-70-2 (Calcium)
CN 0 (2-chloro-**N(6)**-(**3-iodobenzyl**)-**5'-N-methylcarboxamidoadenosine**); 0

(Antibodies); 0 (Antigens, CD95); 0 (Protein p53); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**); EC 3.1.4.3 (Phospholipase C)

L40 ANSWER 4 OF 19 MEDLINE
AN 2002082655 MEDLINE
DN 21669064 PubMed ID: 11809867
TI A(3) **adenosine receptors** in human neutrophils and promyelocytic HL60 cells: a pharmacological and biochemical study.
AU Gessi Stefania; Varani Katia; Merighi Stefania; Cattabriga Elena; Iannotta Valeria; Leung Edward; Baraldi Pier Giovanni; Borea Pier Andrea
CS Department of Clinical and Experimental Medicine, University of Ferrara, Italy.
SO MOLECULAR PHARMACOLOGY, (2002 Feb) 61 (2) 415-24.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020128
Last Updated on STN: 20020208
Entered Medline: 20020207
AB This work compares the pharmacological and biochemical properties of A(3) **adenosine receptors** in human polymorphonuclear neutrophil granulocytes (PMNs) and promyelocytic HL60 cells. The gene expression of A(3) **receptors** was examined by reverse transcription-polymerase chain reaction experiments, whereas the amount of A(3) subtype on the plasma membrane was quantified by using the high-affinity and selective A(3) antagonist [(3)H]5N-(4-methoxyphenyl-carbamoyl)amino-8-propyl-2-(2-furyl)pyrazolo-[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine ([(3)H]MRE 3008F20). Saturation experiments reveal a single high-affinity binding site with K(D) values of 2.3 +/- 0.3, 2.6 +/- 0.4 nM, and B(max) values of 430 +/- 35, 345 +/- 31 fmol/mg of protein for PMNs and HL60 cells, respectively. Competition of radioligand binding by **adenosine** ligands displays a rank order of potency typical of the A(3) subtype. EC(50) values of N(6)-(3-iodo-benzyl)-2-chloro-**adenosine**-5'-N-methyluronamide (**Cl-IB-MECA**) for inhibition of cAMP levels via A(3) **receptors** are in good agreement with the binding data; furthermore, the response is potently inhibited by MRE 3008F20. In contrast, the high micromolar concentrations of **Cl-IB-MECA** and MRE 3008F20 in stimulating and blocking Ca(2+) mobilization, respectively, are not completely consistent with the involvement of an A(3) **receptor**. Furthermore, an important finding of this work is that the inhibition of PMNs oxidative burst is predominantly A(2A)-mediated, even though an effect of A(3) subtype could not be excluded. This conclusion is based on potent blockade of **Cl-IB-MECA**-mediated inhibition of oxidative burst by SCH 58261 and a minor but significant blockade by MRE 3008F20. In conclusion, HL60 cells express A(3) **receptors** similar to those in PMNs, thus providing a useful model for investigation of biochemical pathways leading to A(3) **receptor** activation.
CT Check Tags: Human
*Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Binding, Competitive
Biological Transport
Calcium: ME, metabolism
Cyclic AMP: ME, metabolism
Gene Expression: DE, drug effects
Granulocytes: DE, drug effects
*Granulocytes: ME, metabolism

HL-60 Cells
Neutrophils: DE, drug effects
*Neutrophils: ME, metabolism
*Phenylurea Compounds: PD, pharmacology
Receptors, Purinergic P1: AI, antagonists & inhibitors
Receptors, Purinergic P1: GE, genetics
***Receptors, Purinergic P1: ME, metabolism**
Superoxides: AI, antagonists & inhibitors
*Triazoles: PD, pharmacology
RN 11062-77-4 (Superoxides); **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; 58-61-7 (Adenosine); 60-92-4 (Cyclic AMP); 7440-70-2 (Calcium)
CN 0 (MRE 3008-F20); 0 (Phenylurea Compounds); 0 (Receptors, Purinergic P1); 0 (Triazoles); 0 (**adenosine A3 receptor**)

L40 ANSWER 5 OF 19 MEDLINE
AN 2001675599 MEDLINE
DN 21560304 PubMed ID: 11704641
TI Pharmacological and biochemical characterization of **adenosine receptors** in the human malignant melanoma **A375** cell line.
AU Merighi S; Varani K; Gessi S; Cattabriga E; Iannotta V; Ulouglu C; Leung E; Borea P A
CS Department of Clinical and Experimental Medicine, Pharmacology Unit, University of Ferrara, Centro Nazionale Di Eccellenza Per Lo Sviluppo Di Metodologie Innovative Per Lo Studio Ed Il Trattamento Delle Patologie Infiammatorie, Italy.
SO BRITISH JOURNAL OF PHARMACOLOGY, **(2001 Nov)** 134 (6) 1215-26. Journal code: 7502536. ISSN: 0007-1188.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20011128
Last Updated on STN: 20020317
Entered Medline: 20020315
AB 1. The present work characterizes, from a pharmacological and biochemical point of view, **adenosine receptors** in the human malignant melanoma **A375** cell line. 2. **Adenosine receptors** were detected by RT - PCR experiments. A1 **receptors** were characterized using [3H]-DPCPX binding with a KD of 1.9+/-0.2 nM and Bmax of 23+/-7 fmol x mg(-1) of protein. A2A **receptors** were studied with [3H]-SCH 58261 binding and revealed a KD of 5.1+/-0.2 nM and a Bmax of 220+/-7 fmol x mg(-1) of protein. **A3 receptors** were studied with the new **A3 adenosine receptor** antagonist [3H]-MRE 3008F20, the only **A3** selective radioligand currently available. Saturation experiments revealed a single high affinity binding site with KD of 3.3+/-0.7 nM and Bmax of 291+/-50 fmol x mg(-1) of protein. 3. The pharmacological profile of radioligand binding on **A375** cells was established using typical **adenosine** ligands which displayed a rank order of potency typical of the different **adenosine receptor** subtype. 4. Thermodynamic data indicated that radioligand binding to **adenosine receptor** subtypes in **A375** cells was entropy- and enthalpy-driven. 5. In functional assays the high affinity A2A agonists HE-NECA, CGS 21680 and A2A - A2B agonist NECA were able to increase cyclic AMP accumulation in **A375** cells whereas **A3** agonists **Cl-IB-MECA**, **IB-MECA** and NECA were able to stimulate Ca2+ mobilization. In conclusion, all these data indicate, for the first time, that **adenosine receptors** with a pharmacological and biochemical profile typical of the A1, A2A, A2B and **A3**

receptor subtype are present on **A375** melanoma cell line.

CT Check Tags: Human
Adenosine Deaminase: ME, metabolism
Binding, Competitive
Calcium: ME, metabolism
Cell Membrane: ME, metabolism
Cyclic AMP: ME, metabolism
***Melanoma, Experimental: ME, metabolism**
Phenylurea Compounds: CH, chemistry
*Phenylurea Compounds: PD, pharmacology
Pyrimidines: CH, chemistry
*Pyrimidines: PD, pharmacology
Radioligand Assay
***Receptors, Purinergic P1: AI, antagonists & inhibitors**
Receptors, Purinergic P1: CH, chemistry
Reverse Transcriptase Polymerase Chain Reaction
***Skin Neoplasms: ME, metabolism**
Triazoles: CH, chemistry
*Triazoles: PD, pharmacology
Tritium
Tumor Cells, Cultured
Xanthines: CH, chemistry
*Xanthines: PD, pharmacology

RN 10028-17-8 (Tritium); 102146-07-6 (1,3-dipropyl-8-cyclopentylxanthine); 60-92-4 (Cyclic AMP); 7440-70-2 (Calcium)

CN 0 (MRE 3008-F20); 0 (Phenylurea Compounds); 0 (Pyrimidines); 0 (Receptors, Purinergic P1); 0 (SCH 58261); 0 (Triazoles); 0 (Xanthines); EC 3.5.4.4 (Adenosine Deaminase)

L40 ANSWER 6 OF 19 MEDLINE
AN 2001524195 MEDLINE
DN 21455377 PubMed ID: 11570815
TI The **A3 adenosine receptor** as a new target for cancer therapy and chemoprotection.
AU Fishman P; Bar-Yehuda S; Barer F; Madi L; Multani A S; Pathak S
CS Laboratory of Clinical and Tumor Immunology, Rabin Medical Center, Petach-Tikva, 49100, Israel.. pfishman@post.tau.ac.il
SO EXPERIMENTAL CELL RESEARCH, **(2001 Oct 1)** 269 (2) 230-6. Journal code: 0373226. ISSN: 0014-4827.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200111
ED Entered STN: 20010926
Last Updated on STN: 20011105
Entered Medline: 20011101

AB **Adenosine**, a purine nucleoside, acts as a regulatory molecule, by binding to specific G-protein-coupled A(1), A(2A), A(2B), and **A(3)** cell surface **receptors**. We have recently demonstrated that **adenosine** induces a differential effect on tumor and normal cells. While inhibiting in vitro tumor cell growth, it stimulates bone marrow cell proliferation. This dual activity was mediated through the **A3 adenosine receptor**. This study showed that a synthetic agonist to the **A3 adenosine receptor**, 2-chloro-N(6)-(3-iodobenzyl)-**adenosine**-5'-N-methyl-uronamide (**Cl-IB-MECA**), at nanomolar concentrations, inhibited tumor cell growth through a cytostatic pathway, i.e., induced an increase number of cells in the G0/G1 phase of the cell cycle and decreased the telomeric signal. Interestingly, **Cl-IB-MECA** stimulates murine bone marrow cell proliferation through the induction of granulocyte-colony-stimulating factor. Oral administration of **Cl**

-IB-MECA to melanoma-bearing mice suppressed the development of melanoma lung metastases (60.8 +/- 6.5% inhibition). In combination with cyclophosphamide, a synergistic anti-tumor effect was achieved (78.5 +/- 9.1% inhibition). Furthermore, **Cl-IB -MECA** prevented the cyclophosphamide-induced myelotoxic effects by increasing the number of white blood cells and the percentage of neutrophils, demonstrating its efficacy as a chemoprotective agent. We conclude that **A3 adenosine receptor** agonist, **Cl-IB-MECA**, exhibits systemic anticancer and chemoprotective effects.

CT Check Tags: Animal; Male
Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Administration, Oral
Antineoplastic Agents, Alkylating: PD, pharmacology
Bone Marrow Cells: ME, metabolism
Cell Cycle
Cell Division
Cyclophosphamide: PD, pharmacology
Granulocyte Colony-Stimulating Factor: ME, metabolism
Granulocyte-Macrophage Colony-Stimulating Factor: ME, metabolism
In Situ Hybridization, Fluorescence
Lung Neoplasms: PC, prevention & control
Lung Neoplasms: SC, secondary
Mice
Mice, Inbred C57BL
***Neoplasms: PC, prevention & control**
***Neoplasms: TH, therapy**
Neoplasms, Experimental
Protein Binding
***Receptors, Purinergic P1: ME, metabolism**
Telomere: ME, metabolism
Tumor Cells, Cultured

RN 143011-72-7 (Granulocyte Colony-Stimulating Factor); 50-18-0 (Cyclophosphamide); 58-61-7 (Adenosine); 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

CN 0 (2-chloro-**N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine**); 0 (Antineoplastic Agents, Alkylating); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**)

L40 ANSWER 7 OF 19 MEDLINE
AN 2001505637 MEDLINE
DN 21413486 PubMed ID: 11522605
TI Pharmacological characterization of **adenosine receptors** in PGT-beta mouse pineal gland tumour cells.
AU Suh B C; Kim T D; Lee J U; Seong J K; Kim K T
CS Department of Life Science, Division of Molecular and Life Science, Pohang University of Science and Technology, San 31, Hyoja-Dong, Pohang 790-784, Korea.
SO BRITISH JOURNAL OF PHARMACOLOGY, **(2001 Sep)** 134 (1) 132-42.
Journal code: 7502536. ISSN: 0007-1188.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010917
Last Updated on STN: 20011015
Entered Medline: 20011011
AB 1. The **adenosine receptor** in mouse pinealocytes was identified and characterized using pharmacological and physiological

approaches. 2. Expression of the two **adenosine receptor** subtypes A2B and **A3** was detected in mouse pineal glands and PGT-beta cells by polymerase chain reaction and nucleotide sequencing. 3. **Adenosine** and 5'-N-ethylcarboxamidoadenosine (NECA) evoked cyclic AMP generation but the A2)-selective agonist 2-(4-(2-carboxyethyl)phenylethylamino)**adenosine**-5'-N-ethylcarboxamideadenosine (CGS 21680) and the A1-specific agonists R-N(6)-(2-phenylisopropyl)**adenosine** (R-PIA) and N(6)-cyclopentyladenosine (CPA) had little effect on intracellular cyclic AMP levels. The A2B **receptor** selective antagonists alloxazine and enprofylline completely blocked NECA-mediated cyclic AMP accumulation. 4. Treatment of cells with the **A3**-selective agonist N(6)-(3-iodobenzyl)-5'-(N-methylcarbamoyl)**adenosine** (**IB-MECA**) inhibited the elevation of the cyclic AMP level induced by NECA or isoproterenol in a concentration-dependent manner with maximal inhibition of 40 - 50%. These responses were blocked by the specific **A3 adenosine receptor** antagonist MRS 1191. Pretreatment of the cells with pertussis toxin attenuated the **IB-MECA**-induced responses, suggesting that this effect occurred via the pertussis toxin-sensitive inhibitory G proteins. 5. **IB-MECA** also caused a concentration-dependent elevation in [Ca(2+)]i and IP3 content. Both the responses induced by **IB-MECA** were attenuated by treatment with U73122 or phorbol 12-myristate 13-acetate. 6. These data suggest the presence of both A2B and **A3 adenosine receptors** in mouse pineal tumour cells and that the A2B **receptor** is positively coupled to adenylyl cyclase whereas the **A3 receptor** is negatively coupled to adenylyl cyclase and also coupled to phospholipase C.

CT Check Tags: Animal; Support, Non-U.S. Gov't
*Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Adenosine Triphosphate: PD, pharmacology
Adenosine-5'-(N-ethylcarboxamide): PD, pharmacology
Adenylate Cyclase: ME, metabolism
Calcium: ME, metabolism
Cyclic AMP: ME, metabolism
Dihydropyridines: PD, pharmacology
Dose-Response Relationship, Drug
Enzyme Activation: DE, drug effects
Estrenes: PD, pharmacology
Forskolin: PD, pharmacology
GTP-Binding Proteins: DE, drug effects
GTP-Binding Proteins: ME, metabolism
Gene Expression Regulation, Neoplastic: DE, drug effects
Inositol 1,4,5-Trisphosphate: ME, metabolism
Isoproterenol: PD, pharmacology
Mice
Mice, Inbred CBA
Pertussis Toxins: PD, pharmacology
Phospholipases: ME, metabolism
***Pinealoma: ME, metabolism**
Pinealoma: PA, pathology
Pyrrolidinones: PD, pharmacology
RNA, Messenger: DE, drug effects
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
***Receptors, Purinergic P1: DE, drug effects**
Receptors, Purinergic P1: GE, genetics
Receptors, Purinergic P1: PH, physiology
Ro 20-1724: PD, pharmacology
Tetradecanoylphorbol Acetate: PD, pharmacology
Time Factors
Tumor Cells, Cultured

RN 112648-68-7 (U 73122); **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; 16561-29-8 (Tetradecanoylphorbol Acetate); 29925-17-5 (Ro 20-1724); 35920-39-9 (Adenosine-5'-(N-ethylcarboxamide)); 56-65-5 (Adenosine Triphosphate); 58-61-7 (Adenosine); 60-92-4 (Cyclic AMP); 66428-89-5 (Forskolin); 70323-44-3 (Pertussis Toxins); 7440-70-2 (Calcium); 7683-59-2 (Isoproterenol); 85166-31-0 (Inositol 1,4,5-Trisphosphate)
CN 0 (Dihydropyridines); 0 (Estrenes); 0 (MRS 1191); 0 (Pyrrolidinones); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1); 0 (**adenosine** A2B **receptor**); 0 (**adenosine A3 receptor**)
; EC 3.1.- (Phospholipases); EC 3.6.1.- (GTP-Binding Proteins); EC 4.6.1.1 (Adenylate Cyclase)

L40 ANSWER 8 OF 19 MEDLINE
AN 2001505636 MEDLINE
DN 21413484 PubMed ID: 11522603
TI Pharmacological and biochemical characterization of **A3 adenosine receptors** in Jurkat T cells.
AU Gessi S; Varani K; Merighi S; Morelli A; Ferrari D; Leung E; Baraldi P G; Spalluto G; Borea P A
CS Department of Clinical and Experimental Medicine, Pharmacology Unit, University of Ferrara, Italy.
SO BRITISH JOURNAL OF PHARMACOLOGY, **(2001 Sep)** 134 (1) 116-26.
Journal code: 7502536. ISSN: 0007-1188.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010917
Last Updated on STN: 20011015
Entered Medline: 20011011
AB 1. The present work was devoted to the study of **A3 adenosine receptors** in Jurkat cells, a human leukemia line. 2. The **A3** subtype was found by means of RT-PCR experiments and characterized by using the new **A3 adenosine receptor** antagonist [3H]-MRE 3008F20, the only **A3** selective radioligand currently available. Saturation experiments revealed a single high affinity binding site with K(D) of 1.9+/-0.2 nM and B(max) of 1.3+/-0.1 pmol mg(-1) of protein. 3. The pharmacological profile of [3H]-MRE 3008F20 binding on Jurkat cells was established using typical **adenosine** ligands which displayed a rank order of potency typical of the **A3** subtype. 4. Thermodynamic data indicated that [3H]-MRE 3008F20 binding to **A3** subtype in Jurkat cells was entropy- and enthalpy-driven, according with that found in cells expressing the recombinant human **A3** subtype. 5. In functional assays the high affinity **A3** agonists **Cl-IB-MECA** and **IB-MECA** were able to inhibit cyclic AMP accumulation and stimulate Ca(2+) release from intracellular Ca(2+) pools followed by Ca(2+) influx. 6. The presence of the other **adenosine** subtypes was investigated in Jurkat cells. A1 **receptors** were characterized using [3H]-DPCPX binding with a K(D) of 0.9+/-0.1 nM and B(max) of 42+/-3 fmol mg(-1) of protein. A2A **receptors** were studied with [3H]-SCH 58261 binding and revealed a K(D) of 2.5+/-0.3 nM and a B(max) of 1.4+/-0.2 pmol mg(-1) of protein. 7. In conclusion, by means of the first antagonist radioligand [3H]-MRE 3008F20 we could demonstrate the existence of functional **A3 receptors** on Jurkat cells.
CT Check Tags: Animal; Human
Binding, Competitive: DE, drug effects
CHO Cells
Calcium: ME, metabolism
Cyclic AMP: ME, metabolism

Dose-Response Relationship, Drug
Guanosine Triphosphate: PD, pharmacology
Hamsters
Jurkat Cells
Kinetics
Phenylurea Compounds: ME, metabolism
Phenylurea Compounds: PD, pharmacology
Pyrimidines: ME, metabolism
Pyrimidines: PD, pharmacology
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
Receptors, Purinergic P1: AG, agonists
***Receptors, Purinergic P1: GE, genetics**
Receptors, Purinergic P1: ME, metabolism
Reverse Transcriptase Polymerase Chain Reaction
T-Lymphocytes: CY, cytology
T-Lymphocytes: DE, drug effects
*T-Lymphocytes: ME, metabolism
Thermodynamics
Time Factors
Triazoles: ME, metabolism
Triazoles: PD, pharmacology
Tritium: DU, diagnostic use
Xanthines: ME, metabolism
Xanthines: PD, pharmacology

RN 10028-17-8 (Tritium); 102146-07-6 (1,3-dipropyl-8-cyclopentylxanthine); 60-92-4 (Cyclic AMP); 7440-70-2 (Calcium); 86-01-1 (Guanosine Triphosphate)

CN 0 (MRE 3008-F20); 0 (Phenylurea Compounds); 0 (Pyrimidines); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1); 0 (SCH 58261); 0 (Triazoles); 0 (Xanthines); 0 (**adenosine** A(2a) **receptor**); 0 (**adenosine A3 receptor**)

L40 ANSWER 9 OF 19 MEDLINE

AN 2001413561 MEDLINE

DN 21355982 PubMed ID: 11462805

TI The **A3 adenosine receptor** induces cytoskeleton rearrangement in human astrocytoma cells via a specific action on Rho proteins.

AU Abbracchio M P; Camurri A; Ceruti S; Cattabeni F; Falzano L; Giammarioli A M; Jacobson K A; Trincavelli L; Martini C; Malorni W; Fiorentini C

CS Department of Pharmacological Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy.. Mariapia.Abbracchio@unimi.it

SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(2001 Jun)** 939 63-73.
Journal code: 7506858. ISSN: 0077-8923.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200108

ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB In previous studies, we have demonstrated that exposure of astroglial cells to **A3 adenosine receptor** agonists results in dual actions on cell survival, with "trophic" and antiapoptotic effects at nanomolar concentrations and induction of cell death at micromolar agonist concentrations. The protective actions of **A3** agonists have been associated with a reinforcement of the actin cytoskeleton, which likely results in increased resistance of cells to cytotoxic stimuli. The molecular mechanisms at the basis of this effect and the signalling pathway(s) linking the **A3 receptor**

to the actin cytoskeleton have never been elucidated. Based on previous literature data suggesting that the actin cytoskeleton is controlled by small GTP-binding proteins of the Rho family, in the study reported here we investigated the involvement of these proteins in the effects induced by **A3** agonists on human astrocytoma ADF cells. The presence of the **A3 adenosine receptor** in these cells has been confirmed by immunoblotting analysis. As expected, exposure of human astrocytoma ADF cells to nanomolar concentrations of the selective **A3** agonist **2-chloro-N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide** (**CI-IB-MECA**) resulted in formation of thick actin positive stress fibers. Preexposure of cells to the C3B toxin that inactivates Rho-proteins completely prevented the actin changes induced by **CI-IB-MECA**. Exposure to the **A3** agonist also resulted in significant reduction of Rho-GDI, an inhibitory protein known to maintain Rho proteins in their inactive state, suggesting a potentiation of Rho-mediated effects. This effect was fully counteracted by the concomitant exposure to the selective **A3 receptor** antagonist MRS1191. These results suggest that the reinforcement of the actin cytoskeleton induced by **A3 receptor** agonists is mediated by an interference with the activation/inactivation cycle of Rho proteins, which may, therefore, represent a biological target for the identification of novel neuroprotective strategies.

CT Check Tags: Human; Support, Non-U.S. Gov't
Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
***Astrocytoma: ME, metabolism**
Cytoskeleton: DE, drug effects
*Cytoskeleton: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Guanine Nucleotide Dissociation Inhibitors: DE, drug effects
*Guanine Nucleotide Dissociation Inhibitors: ME, metabolism
Receptors, Purinergic P1: DE, drug effects
***Receptors, Purinergic P1: ME, metabolism**

RN 133312-85-3 (rhoB p20 GDI); **163042-96-4 (2-chloro-N(6)-(3-iodobenzyl)adenosine-5'-N-methyluronamide)**; 58-61-7 (Adenosine)

CN 0 (Enzyme Inhibitors); 0 (Guanine Nucleotide Dissociation Inhibitors); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**)

L40 ANSWER 10 OF 19 MEDLINE
AN 2001094428 MEDLINE
DN 20574584 PubMed ID: 11125027
TI **A3 adenosine receptor** activation triggers phosphorylation of protein kinase B and protects rat basophilic leukemia 2H3 mast cells from apoptosis.
AU Gao Z; Li B S; Day Y J; Linden J
CS Department of Cardiovascular Medicine, University of Virginia, Charlottesville, Virginia 22908-0466, USA.
NC R01-HL37942 (NHLBI)
SO MOLECULAR PHARMACOLOGY, **(2001 Jan)** 59 (1) 76-82.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125
AB **Adenosine** accumulates to high levels in inflamed or ischemic tissues and activates **A3 adenosine receptors**

(ARs) on mast cells to trigger degranulation. Here we show that stimulation of rat basophilic leukemia (RBL)-2H3 mast-like cells with the **A3** AR agonists N6-(3-iodo)benzyl-5'-N-methylcarboxamidodoadenosine (**IB-MECA**; 10 nM) or inosine (10 microM) stimulates phosphorylation of protein kinase B (Akt). **IB-MECA** (1 microM) also causes a >50% reduction in apoptosis caused by exposure of RBL-2H3 cells to UV light. Akt phosphorylation is not stimulated by 100 nM N6-cyclopentyladenosine (A1-selective) or CGS21680 (A2A-selective) and is absent in cells pretreated with wortmannin or pertussis toxin. The KI values of the AR antagonists BW-1433 and 8-sulfophenyltheophylline (8-SPT) were determined in radioligand binding assays for all four subtypes of rat ARs: BW-1433 (A1, 5.8 +/- 1.0 nM; A2A, 240 +/- 37; A2B, 30 +/- 10; **A3**, 12,300 +/- 3, 700); 8-SPT (A1, 3.2 +/- 1.2 microM; A2A, 57 +/- 4; A2), 2.2 +/- 0.8; **A3**, >100). BW-1433 and the **A3** -selective antagonist MRS1523 (5 microM), but not 8-SPT (100 microM), block **IB-MECA**-induced protection from apoptosis, confirming the **A3** AR as the mediator of the antiapoptotic response. The data suggest that **adenosine** and inosine activate Gi-coupled **A3** ARs to protect mast cells from apoptosis by a pathway involving the betagamma subunits of Gi, phosphatidylinositol 3-kinase beta, and Akt. We speculate that activation of **A3** ARs on mast cells or other cells that express **A3** ARs (e.g., eosinophils) may facilitate their survival and accumulation in inflamed tissues.

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
*Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
*Apoptosis: PH, physiology
Leukemia, Basophilic, Acute: PA, pathology
*Mast Cells: PA, pathology
Mast Cells: RE, radiation effects
Phosphorylation
*Proto-Oncogene Proteins: ME, metabolism
Radioligand Assay
Rats
***Receptors, Purinergic P1: ME, metabolism**
Receptors, Purinergic P1: PH, physiology
Signal Transduction
Tumor Cells, Cultured
Ultraviolet Rays

RN **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; 58-61-7 (Adenosine)

CN 0 (2-chloro-**N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine**); 0 (Proto-Oncogene Proteins); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**); 0 (proto-oncogene protein akt)

L40 ANSWER 11 OF 19 MEDLINE
AN 1999021767 MEDLINE
DN 99021767 PubMed ID: 9802962
TI Evidence that IgE **receptor** stimulation increases **adenosine** release from rat basophilic leukaemia (RBL-2H3) cells.
AU Lloyd H G; Ross L; Li K M; Ludowyke R I
CS Department of Pharmacology, The University of Sydney, Sydney, NSW, 2006, Australia.. hgelloyd@pharmacol.su.oz.au
SO PULMONARY PHARMACOLOGY AND THERAPEUTICS, **(1998 Feb)** 11 (1) 41-6. Journal code: 9715279. ISSN: 1094-5539.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902

ED Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990211

AB **Adenosine** may play a role in asthma by enhancing inflammatory mediator release from lung mast cells. In this study, we investigated whether **adenosine** is released from cultured rat basophilic leukaemia (RBL-2H3) cells in response to antigen challenge and whether released **adenosine** enhances mediator release. RBL-2H3 cells closely resemble mucosal mast cells, the most common type of mast cell in lung tissue, and they express **adenosine A3 receptors** (which have been associated with asthma). Measurement of **adenosine** in RBL-2H3 cell incubation medium was possible if **adenosine** metabolism was inhibited by EHNA (10 microM; an **adenosine** deaminase inhibitor) and 5-iodotubericidin (5-IT; 10 microM; an **adenosine** kinase inhibitor). Basal **adenosine** concentration increased up to 1.0 microM during a 90 min incubation; after antigen challenge, **adenosine** concentration was increased by 0.3-0.4 microM above basal. Antigen-induced **adenosine** release ranged from 30-70 nmol/1.25x10(6) cells. Antigen-induced mediator release (beta-hexosaminidase and [3H]5-hydroxytryptamine) was increased by **APNEA**, an **adenosine A3 receptor** agonist (EC50 approximately 20 nm) but inhibited by EHNA and 5-IT, despite increased **adenosine** levels. This inhibition was not blocked by the **adenosine** A1/A2 **receptor** antagonist DPSPX (5 microM). Therefore, it is unlikely to be related to **adenosine receptor** activation. In conclusion, although our data provide no direct support for a positive feedback effect of **adenosine** on mast cell mediator release, the observation that IgE **receptor** stimulation increases **adenosine** production in cells which express stimulatory **A3 receptors** is consistent with this hypothesis.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Adenine: AA, analogs & derivatives
Adenine: PD, pharmacology
Adenosine: AA, analogs & derivatives
Adenosine: ME, metabolism
Adenosine: PD, pharmacology
*Adenosine: SE, secretion
Cytoplasmic Granules: ME, metabolism
Leukemia, Basophilic, Acute
Mast Cells: DE, drug effects
Mast Cells: EN, enzymology
*Mast Cells: ME, metabolism
Rats
*Receptors, IgE: ME, metabolism
Receptors, Purinergic P1: AG, agonists
Serotonin: ME, metabolism
Tubercidin: AA, analogs & derivatives
Tubercidin: PD, pharmacology
Tumor Cells, Cultured
beta-N-Acetylhexosaminidase: ME, metabolism

RN 24386-93-4 (5-iodotubercidin); 50-67-9 (Serotonin); 58-61-7 (Adenosine); 59262-86-1 (9-(2-hydroxy-3-nonyl)adenine); 69-33-0 (Tubercidin); 73-24-5 (Adenine)

CN 0 (**N(6)-2-(4-aminophenyl)ethyladenosine**); 0 (Receptors, IgE); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**); EC 3.2.1.52 (beta-N-Acetylhexosaminidase)

L40 ANSWER 12 OF 19 MEDLINE
AN 1998339371 MEDLINE
DN 98339371 PubMed ID: 9676749

TI Apoptosis by 2-chloro-2'-deoxy-adenosine and 2-chloro-adenosine in human peripheral blood mononuclear cells.

AU Barbieri D; Abbracchio M P; Salvioli S; Monti D; Cossarizza A; Ceruti S; Brambilla R; Cattabeni F; Jacobson K A; Franceschi C
CS Department of Biomedical Sciences, University of Modena, Italy.

NC N01MH30003 (NIMH)
SO NEUROCHEMISTRY INTERNATIONAL, **(1998 May-Jun)** 32 (5-6) 493-504. Journal code: 8006959. ISSN: 0197-0186.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19980925

AB **Adenosine** has profound effects on immune cells and has been implicated in the intrathymic apoptotic deletion of T-cells during development. In order to characterize **adenosine** effects on quiescent peripheral blood mononuclear cells (PBMC), we have evaluated the ability of the previously characterized **adenosine** **receptor** agonist 2-chloro-**adenosine** (2CA; Ceruti, Barbieri et al., 1997) and of the antineoplastic drug 2-chloro-2'-deoxy-**adenosine** (2CdA, cladribine) to trigger apoptosis of PBMC. Apoptosis was assessed by morphological changes, DNA fragmentation by agarose gel electrophoresis and appearance of hypodiploid DNA peak by flow cytometry. 2CA (10 microM) and 2CdA (1 microM) induced apoptosis in human PBMC, which are relatively insensitive to apoptosis. For both agents, the effect was concentration- and time-dependent, although 2CdA induced apoptosis more potently than 2CA. Evaluation of mitochondrial function in parallel samples using the mitochondrial membrane-potential-specific dye JC-1 showed that mitochondrial damage followed the same kinetics as apoptosis, hence an early damage of mitochondria is likely not responsible for **adenosine**-induced death of PBMC. The effect of 2CA was partially prevented by addition of dipyridamole (DP), a nucleoside transport inhibitor, hence some of the apoptotic effect of this nucleoside is, at least in part, due to intracellular action. Alternatively, DP did not affect 2CdA-induced apoptosis, suggesting that 2CdA may enter cells via a DP-insensitive transporter. 5-Iodotubercidin (5-Itu), a nucleoside kinase inhibitor, was also able to partially prevent the action of 2CA and was not able to affect 2CdA-induced apoptosis, suggesting a different role for phosphorylation in 2CA- vs 2CdA-induced apoptosis. To test the role of P1 **receptors**, agonists and antagonists selective at various P1 **receptor** subtypes were used. Data suggest that, for 2CA, apoptosis is partially sustained by activation of the A2A **receptor** subtype, whereas no role is exerted by P1 **receptors** in 2CdA-dependent apoptosis. Moreover, in these cells, apoptosis could also be triggered through intense activation of the **A3** **receptor** via selective agonists such as **2-chloro** **-N6-(3-iodobenzyl)adenosine-** **5'-N-methyluronamide (Cl-IB** **-MECA)**, but this mechanism plays no role in either 2CA- or 2CdA-induced apoptosis. On the whole, our results suggest that 2CA and 2CdA follow different pathways in inducing apoptosis of immune cells. Moreover, our data also suggest that there are at least three different ways by which **adenosine** derivatives may induce apoptosis of human PBMC: (i) through an A2A-like extracellular membrane **receptor**; (ii) through entry of nucleosides into cells and direct activation of intracellular events involved in the apoptotic process; or (iii) through activation of the **A3** **receptor**.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*2-Chloroadenosine: PD, pharmacology
Adenosine: AI, antagonists & inhibitors

Apoptosis: DE, drug effects
*Apoptosis: PH, physiology
Biological Transport: DE, drug effects
Cells, Cultured
*Cladribine: PD, pharmacology
Dipyridamole: PD, pharmacology
Enzyme Inhibitors: PD, pharmacology
*Immunosuppressive Agents: PD, pharmacology
Mitochondria: DE, drug effects
*Monocytes: DE, drug effects
Monocytes: PH, physiology
Nucleosides: AI, antagonists & inhibitors
Nucleosides: ME, metabolism
Receptors, Purinergic P1: PH, physiology
Tubercidin: AA, analogs & derivatives
Tubercidin: PD, pharmacology
Tumor Cells, Cultured
RN 146-77-0 (2-Chloroadenosine); 24386-93-4 (5-iodotubercidin); 4291-63-8 (Cladribine); 58-32-2 (Dipyridamole); 58-61-7 (Adenosine); 69-33-0 (Tubercidin)
CN 0 (Enzyme Inhibitors); 0 (Immunosuppressive Agents); 0 (Nucleosides); 0 (Receptors, Purinergic P1)

L40 ANSWER 13 OF 19 MEDLINE
AN 1998312597 MEDLINE
DN 98312597 PubMed ID: 9650577
TI Activation of the A2A **adenosine receptor** inhibits nitric oxide production in glial cells.
AU Brodie C; Blumberg P M; Jacobson K A
CS Department of Life Science, Bar-Ilan University, Ramat Gan, Israel.. chaya@brosh.cc.biu.ac.il
SO FEBS LETTERS, **(1998 Jun 12)** 429 (2) 139-42.
Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980727
AB Selective **adenosine receptor** agonists and antagonists have marked effects on the outcome of cerebral ischemia, and **adenosine receptors** are expressed on astrocytes. In this study we examined the effects of various **adenosine receptor** agonists on the production of nitric oxide and the induction of iNOS in astrocytes activated by LPS/IFN-gamma and TNF-alpha/IL-1beta and on the production of TNF-alpha. Treatment of the cells with the A2A **receptor** agonist CGS 21680 inhibited both NO production and iNOS expression induced by stimulation with either LPS/IFN-gamma or TNF-alpha/IL-1beta, whereas the A1 and **A3 receptor** agonists, CPA and **Cl-IB-MECA** , respectively, did not have significant inhibitory effects. The inhibitory effect of the A2A **receptor** agonist was antagonized by the specific A2A **receptor** antagonist CSC. The A2A agonist also exerted a small inhibitory effect on the production of TNF-alpha. Similar inhibitory effects on the production of NO were obtained by cyclic AMP-elevating reagents, such as forskolin and dibutyryl cyclic AMP. Our findings suggest that activation of the A2A **receptor** inhibits NO production and iNOS expression likely via increased cAMP.
CT Check Tags: Animal
Enzyme Induction
Neuroglia: DE, drug effects

*Neuroglia: ME, metabolism
*Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: BI, biosynthesis
Rats
Receptors, Purinergic P1: AG, agonists
Receptors, Purinergic P1: AI, antagonists & inhibitors
***Receptors, Purinergic P1: ME, metabolism**
Tumor Cells, Cultured
Tumor Necrosis Factor: BI, biosynthesis
RN 10102-43-9 (Nitric Oxide)
CN 0 (Receptors, Purinergic P1); 0 (Tumor Necrosis Factor); 0 (**adenosine** A(2a) **receptor**); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L40 ANSWER 14 OF 19 MEDLINE
AN 1998175324 MEDLINE
DN 98175324 PubMed ID: 9515573
TI Pharmacological characterization of **adenosine** A2B **receptors**: studies in human mast cells co-expressing A2A and A2B **adenosine receptor** subtypes.
AU Feoktistov I; Biaggioni I
CS Department of Medicine, Vanderbilt University, Nashville, TN 37232-2195, USA.
NC R29HL55596 (NHLBI)
RR00095 (NCRR)
SO BIOCHEMICAL PHARMACOLOGY, **(1998 Mar 1)** 55 (5) 627-33.
Journal code: 0101032. ISSN: 0006-2952.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Space Life Sciences
EM 199804
ED Entered STN: 19980416
Last Updated on STN: 20020124
Entered Medline: 19980409
AB Characterization of A2B receptors is hampered by the lack of selective pharmacological probes and often relies on their relative affinity to agonists that are selective at other receptor types. This approach is limited because the affinity of A2B receptors for putative **A3** agonists has not been determined. Using the human erythroleukemia cell line HEL as a cellular model for A2B-mediated adenylate cyclase activation, we found the following potencies (pD2) for the non-selective agonist 5'-N-ethylcarboxamidoadenosine (NECA) (5.65 +/- 0.04), the putative **A3** agonists N6-benzyl-NECA (4.17 +/- 0.06) and N6-(3-iodobenzyl)-N-methyl-5'-carbamoyladenosine (**IB-MECA**) (3.7 +/- 0.02), and the A2A agonist 4-[(N-ethyl-5'-carbamoyladenos-2-yl)-aminoethyl]-phenylpropionic acid (CGS21680) (2.8 +/- 0.1). Because of the lack of a selective agonist, characterization of A2B receptor function is difficult in cells co-expressing A2A receptors. In the human mast cell line HMC-1, NECA induced cAMP accumulation with a concentration-response relationship best fitted to a two-sited model (pD2 7.69 +/- 0.42 and 5.92 +/- 0.21 for high- and low-affinity sites), suggesting the presence of both A2A and A2B receptors in these cells. We demonstrated that A2B receptors can be selectively activated with NECA in the presence of the selective A2A antagonist 5-amino-7-(phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (SCH 58261). Under these conditions, the concentration-response relationship of NECA for cyclic AMP accumulation was now best fitted to a one-site model (pD2 5.68 +/- 0.03, Hill slope 0.93 +/- 0.06, 95% confidence intervals 0.8 to 1.06) corresponding to selective activation of A2B receptors. Using the approaches developed in this study, we determined that A2B, and not A2A or **A3**, receptors account for all the calcium mobilization induced by NECA in HMC-1 cells.

ST Non-programmatic
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Adenosine-5'-(N-ethylcarboxamide): AA, analogs & derivatives
Adenosine-5'-(N-ethylcarboxamide): PD, pharmacology
Calcium: ME, metabolism
Cyclic AMP: ME, metabolism
Dose-Response Relationship, Drug
*Mast Cells: DE, drug effects
Mast Cells: ME, metabolism
Phenethylamines: PD, pharmacology
Pyrimidines: PD, pharmacology
Receptors, Purinergic P1: CL, classification
***Receptors, Purinergic P1: DE, drug effects**
Receptors, Purinergic P1: PH, physiology
Triazoles: PD, pharmacology
Tumor Cells, Cultured
RN 120225-54-9 (CGS 21680); 35920-39-9 (Adenosine-5'-(N-ethylcarboxamide)); 58-61-7 (Adenosine); 60-92-4 (Cyclic AMP); 7440-70-2 (Calcium)
CN 0 (Phenethylamines); 0 (Pyrimidines); 0 (Receptors, Purinergic P1); 0 (SCH 58261); 0 (Triazoles)

L40 ANSWER 15 OF 19 MEDLINE
AN 1998086346 MEDLINE
DN 98086346 PubMed ID: 9425266
TI The **A3 adenosine receptor** mediates cell spreading, reorganization of actin cytoskeleton, and distribution of Bcl-XL: studies in human astroglioma cells.
AU Abbracchio M P; Rainaldi G; Giammarioli A M; Ceruti S; Brambilla R; Cattabeni F; Barbieri D; Franceschi C; Jacobson K A; Malorni W
CS Institute of Pharmacological Sciences, Milan, Italy.
NC 1MH30003 (NIMH)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Dec 18)** 241 (2) 297-304.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980206
Last Updated on STN: 20000303
Entered Medline: 19980126
AB The pathophysiological role of the **adenosine A3 receptor** in the central nervous system is largely unknown. We have investigated the effects of the selective **A3 receptor** agonist 2-chloro-N6-(3-iodobenzyl)-**adenosine, Cl-IB-MECA**, in cells of the astroglial lineage (human astrocytoma ADF cells). A marked reorganization of the cytoskeleton, with appearance of stress fibers and numerous cell protrusions, was found following exposure of cells to low (nM) concentrations of **Cl-IB-MECA**. These "trophic" effects were accompanied by induction of the expression of Rho, a small GTP-binding protein, which was virtually absent in control cells, and by changes of the intracellular distribution of the antiapoptotic protein Bcl-XL, that, in agonist-exposed cells, became specifically associated to cell protrusions. This is the first demonstration that the intracellular organization of Bcl-XL can be modulated by the activation of a G-protein-coupled membrane **receptor**, such as the **A3 adenosine receptor**. Moreover, modulation of the astrocytic cytoskeleton by **adenosine** may have intriguing implications in both nervous system development and in the response of the brain to trauma and ischemia.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Actins: ME, metabolism
Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Astrocytes: DE, drug effects
*Astrocytes: UL, ultrastructure
Astrocytoma
Cell Size
Cytoskeleton: DE, drug effects
*Cytoskeleton: ME, metabolism
GTP-Binding Proteins: ME, metabolism
*Proto-Oncogene Proteins c-bcl-2: ME, metabolism
Receptors, Purinergic P1: AG, agonists
***Receptors, Purinergic P1: ME, metabolism**
Tumor Cells, Cultured
RN 58-61-7 (Adenosine)
CN 0 (2-chloro-**N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine**); 0 (Actins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Receptors, Purinergic P1); 0 (**adenosine A3 receptor**); 0 (bcl-x protein); EC 3.6.1.- (GTP-Binding Proteins)

L40 ANSWER 16 OF 19 MEDLINE
AN 1998016259 MEDLINE
DN 98016259 PubMed ID: 9351976
TI Canine mast cell **adenosine receptors**: cloning and expression of the **A3 receptor** and evidence that degranulation is mediated by the A2B **receptor**.
AU Auchampach J A; Jin X; Wan T C; Caughey G H; Linden J
CS Departments of Medicine (Cardiology), University of Virginia, Charlottesville, Virginia 22908, USA.
NC HL37942 (NHLBI)
T32-HL07284 (NHLBI)
SO MOLECULAR PHARMACOLOGY, **(1997 Nov)** 52 (5) 846-60.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U54792
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971124
AB We cloned and characterized the canine **A3 adenosine receptor** (AR) and examined AR-induced degranulation of the BR line of canine mastocytoma cells. Canine **A3AR** transcript is found predominantly in spleen, lung, liver, and testes and encodes a 314-amino acid heptahelical **receptor**. 125I-N6-Aminobenzyladenosine binds to two affinity states of canine **A3AR** with KD values of 0.7 +/- 0.1 and 16 +/- 0.8 nM, reflecting G protein-coupled and -uncoupled **receptors**, respectively. Xanthine antagonists bind with similar affinities to human, canine, and rabbit **receptors** but with 80-400-fold lower affinities to rat **A3AR**. Although canine BR mastocytoma cells contain A1AR, A2BAR, and **A3AR**, degranulation seems to be mediated primarily by A2BARs stimulated by the nonselective agonist 5'-N-ethylcarboxamidoadenosine (NECA) but not by the **A3** -selective agonist N6-(3-iodobenzyl)**adenosine** -5'-N-methylcarboxamide. NECA-stimulated degranulation is not prevented by pertussis toxin and is blocked by enprofylline (Ki = 7 microM), an antiasthmatic xanthine with low affinity (Ki > 100 microM) for A1AR, A2AAR, and **A3AR**. NECA increases canine mastocytoma cell cAMP, Ca2+, and inositol trisphosphate levels; these responses are antagonized

half-maximally by 7-15 microM enprofylline. The results suggest that (i) the cloned canine **A3AR** is structurally and pharmacologically more similar to human than to rat **A3AR**; (ii) the A2BAR, and not the A1AR or **A3AR**, is principally responsible for **adenosine**-mediated degranulation of canine BR mastocytoma cells; and (iii) the BR cell A2BAR couples to both Ca2+ mobilization and cAMP accumulation. Although A2B **receptors** play a major role in the regulation of BR mast cell degranulation, multiple AR subtypes and G proteins may influence mast cell functions.

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.
Adenine: AA, analogs & derivatives
Adenine: PD, pharmacology
Adenosine: AA, analogs & derivatives
Adenosine: PD, pharmacology
Amino Acid Sequence
Base Sequence
COS Cells
Calcium: ME, metabolism
Cercopithecus aethiops
*DNA, Complementary: GE, genetics
DNA, Complementary: ME, metabolism
Dinucleoside Phosphates: PD, pharmacology
Dogs
*Mast Cells: CH, chemistry
Mast Cells: PH, physiology
Molecular Sequence Data
*Neoplasm Proteins: GE, genetics
Neoplasm Proteins: ME, metabolism
Norbornanes: PD, pharmacology
RNA, Messenger: ME, metabolism
***Receptors, Purinergic P1: GE, genetics**
Receptors, Purinergic P1: ME, metabolism
***Sarcoma, Mast-Cell: CH, chemistry**
Sarcoma, Mast-Cell: ME, metabolism
Sequence Alignment
Sequence Homology, Amino Acid
Xanthines: PD, pharmacology
beta-N-Acetylhexosaminidase: ME, metabolism

RN 112533-64-9 (BW A522); **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; 2382-66-3 (cytidylyl adenosine); 58-61-7 (Adenosine); 73-24-5 (Adenine); 7440-70-2 (Calcium)

CN 0 (DNA, Complementary); 0 (Dinucleoside Phosphates); 0 (Neoplasm Proteins); 0 (Norbornanes); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1); 0 (WRC 0571); 0 (Xanthines); 0 (**adenosine A3 receptor**); EC 3.2.1.52 (beta-N-Acetylhexosaminidase)

L40 ANSWER 17 OF 19 MEDLINE
AN 97242183 MEDLINE
DN 97242183 PubMed ID: 9125172
TI **Adenosine A3 receptor** agonists protect HL-60 and U-937 cells from apoptosis induced by **A3** antagonists.
AU Yao Y; Sei Y; Abbracchio M P; Jiang J L; Kim Y C; Jacobson K A
CS Laboratory of Bioorganic Chemistry, NIDDK/NIH, Bethesda, Maryland 20892, USA.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Mar 17)** 232 (2) 317-22.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 19970506

Last Updated on STN: 19980206
Entered Medline: 19970422

AB The effects of novel, selective **adenosine** (ADO) **A3 receptor** antagonists of diverse structure on cells of the human HL-60 leukemia and U-937 lymphoma cell lines were examined. Both 3-ethyl 5-benzyl 2-methyl-6-phenyl-4-phenylethynyl-1,4-(+/-)-dihydropyridine-3, 5-dicarboxylate (MRS 1191, 0.5 microM) and 6-carboxy-methyl-5, 9-dihydro-9-methyl-2-phenyl-[1,2,4]-triazolo [5,1-a][2,7]naphthyridine (L-249313, 0.5 microM) induced apoptotic cell death and expression of bak protein. Low concentrations of the **A3 receptor** agonist **2-chloro-N6-(3-iodobenzyl) adenosine-5'-N-methyluronamide** (**Cl-IB-MECA**, 10 nM or 1 microM) protected against antagonist-induced cell death. At concentrations > or = 10 microM, the agonist alone produced apoptosis and bak expression in various cell lines. It is suggested that there exists a tonic low level of **A3 receptor** activation, possibly induced by release of endogenous **adenosine**, that results in cell protection.

CT Check Tags: Human
Adenosine: AA, analogs & derivatives
*Adenosine: ME, metabolism
Adenosine: PD, pharmacology
*Apoptosis: DE, drug effects
DNA Fragmentation
Dihydropyridines: PD, pharmacology
Dose-Response Relationship, Drug
***HL-60 Cells: DE, drug effects**
HL-60 Cells: PA, pathology
Pyrazoles: PD, pharmacology
Quinazolines: PD, pharmacology
***Receptors, Purinergic P1: AG, agonists**
***Receptors, Purinergic P1: AI, antagonists & inhibitors**
Triazoles: PD, pharmacology

RN 104615-18-1 (9-chloro-2-(2-furyl)-(1,2,4)triazolo(1,5-c)quinazolin-5-imine); 119666-09-0 (AHC 52); **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)**; **163042-96-4 (2-chloro-N(6)-(3-iodobenzyl)adenosine-5'-N-methyluronamide)**; 58-61-7 (Adenosine)

CN 0 (Dihydropyridines); 0 (Pyrazoles); 0 (Quinazolines); 0 (Receptors, Purinergic P1); 0 (Triazoles)

L40 ANSWER 18 OF 19 MEDLINE
AN 96216748 MEDLINE
DN 96216748 PubMed ID: 8645277
TI Induction of apoptosis in HL-60 human promyelocytic leukemia cells by **adenosine A(3) receptor** agonists.
AU Kohno Y; Sei Y; Koshiba M; Kim H O; Jacobson K A
CS Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1996 Feb 27)** 219 (3) 904-10.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960726
Last Updated on STN: 19970203
Entered Medline: 19960715

AB The effects of **adenosine** (ADO) analogs on cells of the human promyelocytic HL-60 line were examined. ADO **A(3) receptor** agonists, N(6)-(3-iodobenzyl)**adenosine** -5'-N-methylcarboxamide (**IB-MECA**, 30-60 microM) and

2-chloro-N(6)-(3-iodobenzyl)adenosine-5'-N-methyluronamide (CI-IB-MECA, 10-30 microM) induced apoptotic cell death. In contrast, neither an A(1)/A(2) antagonist (XAC) nor other selective ADO **receptor** agonists (CPA, NECA and CGS21680) induced apoptosis at concentrations of <30 microM. Both **IB-MECA** and **CI-IB-MECA** significantly induced Ca(2+) release from intracellular Ca(2+) pools followed by Ca(2+) influx, suggesting the presence of phospholipase C-coupled ADO **A(3) receptors** on HL-60 cells. This was further supported by the presence of mRNA of ADO **A3 receptor** in the cells. These results suggest that activation of ADO **A(3) receptors** is responsible for the ADO-induced apoptosis in HL-60 cells and could be of potential therapeutic value in the treatment of leukemia.

CT Check Tags: Human
*Adenosine: AA, analogs & derivatives
*Adenosine: PD, pharmacology
*Apoptosis
Apoptosis: DE, drug effects
Base Sequence
Calcium: ME, metabolism
Cytosol: DE, drug effects
Cytosol: ME, metabolism
DNA Primers
DNA, Neoplasm: DE, drug effects
DNA, Neoplasm: IP, isolation & purification
DNA, Neoplasm: ME, metabolism
Electrophoresis, Agar Gel
HL-60 Cells
Kinetics
Molecular Sequence Data
Polymerase Chain Reaction
RNA, Messenger: AN, analysis
***Receptors, Purinergic P1: AG, agonists**
Receptors, Purinergic P1: BI, biosynthesis
Receptors, Purinergic P1: PH, physiology
Structure-Activity Relationship

RN **152918-18-8 (N(6)-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine)** ; 58-61-7 (Adenosine); 7440-70-2 (Calcium)

CN 0 (DNA Primers); 0 (DNA, Neoplasm); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1)

L40 ANSWER 19 OF 19 MEDLINE
AN 96090479 MEDLINE
DN 96090479 PubMed ID: 7582508
TI The in vitro pharmacology of ZM 241385, a potent, non-xanthine A2a selective **adenosine receptor** antagonist.
AU Poucher S M; Keddie J R; Singh P; Stoggall S M; Caulkett P W; Jones G; Coll M G
CS Cardiovascular and Metabolism Department, ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire.
SO BRITISH JOURNAL OF PHARMACOLOGY, **(1995 Jul)** 115 (6) 1096-102. Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951215
AB 1. This paper describes the in vitro pharmacology of ZM 241385

(4-(2-[7-amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a][1,3,5]triazin- 5-yl amino]ethyl) phenol), a novel non-xanthine **adenosine receptor** antagonist with selectivity for the A2a **receptor** subtype. 2. ZM 241385 had high affinity for A2a **receptors**. In rat phaeochromocytoma cell membranes, ZM 241385 displaced binding of tritiated 5'-N-ethylcarboxamidoadenosine (NECA) with a pIC50 of 9.52, (95% confidence limits, c.l., 9.02-10.02). In guinea-pig isolated Langendorff hearts, ZM 241385 antagonized vasodilatation of the coronary bed produced by 2-chloroadenosine (2-CADO) and 2-[p-(2-carboxyethyl) phenethylamino]-5'-N-ethylcarboxamidoadenosine (CGS21680) with pA2 values of 8.57 (c.l., 8.45-8.68) and 9.02 (c.l., 8.79-9.24) respectively. 3. ZM 241385 had low potency at A2b **receptors** and antagonized the relaxant effects of **adenosine** in the guinea-pig aorta with a pA2 of 7.06, (c.l., 6.92-7.19). 4. ZM 241385 had a low affinity at A1 **receptors**. In rat cerebral cortex membranes it displaced tritiated R-phenylisopropyladenosine (R-PIA) with a pIC50 of 5.69 (c.l., 5.57-5.81). ZM 241385 antagonized the bradycardic action of 2-CADO in guinea-pig atria with a pA2 of 5.95 (c.l., 5.72-6.18). 5. ZM 241385 had low affinity for **A3 receptors**. At cloned rat **A3 receptors** expressed in chinese hamster ovary cells, it displaced iodinated aminobenzyl-5'-N-methylcarboxamido **adenosine** (**AB-MECA**) with a pIC50 of 3.82 (c.l., 3.67-4.06). 6. ZM 241385 had no significant additional pharmacological effects on the isolated tissues used in these studies at concentrations three orders of magnitude greater than those which block A2a **receptors**.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Animal; In Vitro
*Adenosine: PD, pharmacology
Aorta: DE, drug effects
Binding, Competitive
Dose-Response Relationship, Drug
Guinea Pigs
Heart: DE, drug effects
PC12 Cells
Radioligand Assay
Rats
***Receptors, Purinergic P1: AI, antagonists & inhibitors**
RN 58-61-7 (Adenosine)
CN 0 (Receptors, Purinergic P1)

=> fil cancer
FILE 'CANCERLIT' ENTERED AT 13:13:28 ON 21 OCT 2002

FILE COVERS 1963 TO 19 Aug 2002 (20020819/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l60

L60 ANSWER 1 OF 1 CANCERLIT
AN 2002154408 CANCERLIT
DN 22021432 PubMed ID: 11992407
TI Adenosine acts through an A3 receptor to prevent the induction of murine anti-CD3-activated **killer T cells**.
AU Hoskin David W; Butler Jared J; Drapeau Dennis; Haeryfar S M Mansour; Blay Jonathan

CS Department of Microbiology and Immunology, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.. dwhoskin@is.dal.ca
SO INTERNATIONAL JOURNAL OF CANCER, (2002 May 20) 99 (3) 386-95.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002290824
EM 200206
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Adenosine, a purine nucleoside found at high levels in solid tumors, is able to suppress the recognition/adhesion and effector phases of **killer** lymphocyte-mediated tumor **cell** destruction. Here, we demonstrate that adenosine, at concentrations that are typically present in the extracellular fluid of solid tumors, exerts a profound inhibitory effect on the induction of mouse cytotoxic T **cells**, without substantially affecting T-**cell** viability. T-**cell** proliferation in response to mitogenic anti-CD3 antibody was impaired in the presence of 10 microM adenosine (plus coformycin to inhibit endogenous adenosine deaminase). Antigen-specific T-**cell** proliferation was similarly inhibited by adenosine. Anti-CD3-activated **killer** T (AK-T) **cells** induced in the presence of adenosine exhibited reduced major histocompatibility complex-unrestricted cytotoxicity against P815 mastocytoma **cells** in JAM and (51)Cr-release assays. Diminished tumoricidal activity correlated with reduced expression of mRNAs coding for granzyme B, perforin, Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), as well as with diminished Nalpha-CBZ-L-lysine thiobenzylester (BLT) esterase activity. Interleukin-2 and interferon-gamma synthesis by AK-T **cells** was also inhibited by adenosine. AK-T **cells** express mRNA coding for A(2A), A(2B) and A(3) receptors, but little or no mRNA coding for A(1) receptors. The inhibitory effect of adenosine on AK-T **cell** proliferation was blocked by an A(3) receptor antagonist (MRS1191) but not by an A(2) receptor antagonist (3,7-dimethyl-1-propargylxanthine [DMPX]). The A(3) receptor agonists (**N(6)-2-(4-aminophenyl)ethyladenosine** [APNEA] and N(6)-benzyl-5'-N-ethylcarboxamidoadenosine [N(6)-benzyl-NECA]) also inhibited AK-T **cell** proliferation. Adenosine, therefore, acts through an A(3) receptor to prevent AK-T **cell** induction. Tumor-associated adenosine may act through the same mechanism to impair the development of tumor-reactive T **cells** in cancer patients.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*Adenosine: ME, metabolism
Adenosine: PD, pharmacology
Adenosine Deaminase: ME, metabolism
*Antigens, CD3: BI, biosynthesis
Brain: ME, metabolism
Cell Division
Cell Survival
Cells, Cultured
Chromium Radioisotopes: PD, pharmacology
Dose-Response Relationship, Drug
Enzyme-Linked Immunosorbent Assay
Flow Cytometry
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
***Killer Cells: ME, metabolism**
Lymphocytes: ME, metabolism
Membrane Glycoproteins: ME, metabolism
Mice

Mice, Inbred C57BL
Mitochondria: ME, metabolism
RNA, Messenger: ME, metabolism
Receptors, Purinergic P1: AI, antagonists & inhibitors
*Receptors, Purinergic P1: ME, metabolism
Reverse Transcriptase Polymerase Chain Reaction
T-Lymphocytes: ME, metabolism
Tetrazolium Salts: PD, pharmacology
*Theobromine: AA, analogs & derivatives
Theobromine: PD, pharmacology
Thiazoles: PD, pharmacology
Thymidine: ME, metabolism
Tumor Cells, Cultured
Tumor Necrosis Factor: ME, metabolism
RN 14114-46-6 (3,7-dimethyl-1-propargylxanthine); 298-93-1 (thiazolyl blue); 50-89-5 (Thymidine); 58-61-7 (Adenosine); 82115-62-6 (Interferon Type II); 83-67-0 (Theobromine)
CN 0 (Antigens, CD3); 0 (Chromium Radioisotopes); 0 (Interleukin-2); 0 (Membrane Glycoproteins); 0 (RNA, Messenger); 0 (Receptors, Purinergic P1); 0 (TNF-related apoptosis-inducing ligand); 0 (Tetrazolium Salts); 0 (Thiazoles); 0 (Tumor Necrosis Factor); 0 (adenosine A3 receptor); EC 3.5.4.4 (Adenosine Deaminase)

=> d his

(FILE 'HOME' ENTERED AT 12:46:40 ON 21 OCT 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 12:46:54 ON 21 OCT 2002
L1 4 S 163042-96-4 OR 152918-27-9 OR 152918-18-8 OR 89705-21-5

FILE 'MEDLINE' ENTERED AT 12:47:38 ON 21 OCT 2002
L2 63 S L1
L3 122 S AB MECA OR IB MECA OR (CL OR CI)()IB MECA
L4 69 S (N6 OR N 6)()3 IODOBENZYL 5 N METHYLCARBOXAMIDOADENOSINE
L5 27 S 2 CHLORO ()(N6 OR N 6)()3 IODOBENZYL ADENOSINE 5 N METHYLURON
L6 15 S (N6 OR N 6)()4 AMINO 3 IODOBENZYL ADENOSINE 5 N METHYLURONAMI
L7 0 S N 2 4 AMINOPHENYL ETHYLADENOSINE
L8 1 S N 2 4 AMINOPHENYL ETHYL ADENOSINE
L9 8 S (N6 OR N 6)() 2 4 AMINOPHENYL ETHYL ADENOSINE
L10 51 S (N6 OR N 6)() 2 4 AMINOPHENYL ETHYLADENOSINE
L11 16133 S APNEA
L12 44 S L11 AND L2-L10
L13 200 S L2-L10,L12
E NATURAL KILLER/CT
E E4_ALL
E NATURAL KILLER/CT
E E6+ALL
L14 17195 S E2
E E2+ALL
L15 2569 S E34
L16 16171 S E30/BI OR E33/BI
L17 0 S L13 AND L14-L16
L18 1 S KILLER CELL AND L13
E KILLER CELLS/CT
E E3+ALL
L19 3345 S E20+NT
E E32+ALL
L20 4750 S E5+NT
E KILLER CELLS/CT
E E5+ALL
L21 2569 S E21+NT

```
L22        18961 S E20+NT
L23         2569 S E21+NT
L24            1 S L13 AND L19-L23
L25            1 S L18,L24
L26           10 S C4./CT AND L13
                 E TUMOR CELL/CT
                 E E10+ALL
L27       162532 S E8+NT
L28           17 S L13 AND L27
L29           19 S L26,L28,L25
L30           15 S L29 AND PY<=2001
L31           15 S L30 AND ADENOSIN?(L)RECEPTOR?
L32           15 S L31 AND A3
L33            2 S L31 AND A 3
L34           15 S L30-L33
                 E ADENOSINE RECEPTOR/CT
                 E E4+ALL
                 E E2+ALL
L35          185 S L13 AND E12+NT
L36           19 S L35 AND L29
L37           19 S L36 AND A3
L38           19 S L37 AND L2-L37
L39           19 S ADENOSIN?(L)RECEPTOR? AND L38
L40           19 S L39 AND A3?

     FILE 'MEDLINE' ENTERED AT 13:04:04 ON 21 OCT 2002

     FILE 'EMBASE' ENTERED AT 13:04:57 ON 21 OCT 2002
L41           34 S L1
L42           35 S 6 N 2 4 AMINOPHENYL ETHYL ADENOSINE
L43          137 S L3
L44           10 S 2 CHLORO N 6 3 IODOBENZYL ADENOSINE 5 N METHYLURONAMIDE
L45            1 S 1 2 CHLORO 6 3 IODOPHENYL METHYL AMINO 9H PURIN 9 YL 1 DEOXY
L46          171 S L41-L45
L47            2 S NK (L) CELL AND L46
L48            0 S NATURAL(L)KILLER(L)CELL AND L46
                 E NATURAL KILLER CELL/CT
                 E E3+ALL
L49        18570 S E1+NT
L50          418 S E22+NT
L51            0 S L46 AND L49,L50
L52           21 S L46 AND C6.610./CT
L53           15 S L52 AND PY<=2001

     FILE 'CANCERLIT' ENTERED AT 13:11:18 ON 21 OCT 2002
L54           14 S L1
L55           26 S L3
L56           26 S L4-L10
L57            6 S L42,L44,L45
L58           33 S L54-L57
L59            0 S L58 AND NATURAL(L)KILLER(L)CELL
L60            1 S L58 AND KILLER(L)CELL
L61            0 S L58 AND NK

     FILE 'CANCERLIT' ENTERED AT 13:13:28 ON 21 OCT 2002
```